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THE RÔLE OF EMOTION IN DISEASE *

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WHEN your President asked me for the title of the address for this evening, I had in mind some ideas which I wished to elaborate and which could be included under the heading, "The rôle of emotion in disease." The title is so comprehensive, however, that I must set definite limits to the parts of the subject to be considered. This can be done by use of a method time-honored in the history of medicine—the statement and exposition of aphorisms. There are ten of them.

1. *In modern life infections have diminished and nervous strains have increased.* Anyone whose years allow him to survey the events of the last third of a century is aware of profound changes in the conditions of our existence. Among them is a remarkable shift in the importance of common types of illness. Diseases formerly regarded as plagues and pestilences are now largely under control or have almost disappeared. Tuberculosis is no longer "master of the kings of death"; diphtheria has lost most of its terrifying character; the mortality in measles and scarlet fever has gradually been reduced to about a third that of a generation ago; and typhoid and yellow fever, once our arch enemies, may now be regarded as conquered. Release from these and other similar scourges is rightly counted among the great blessings which medicine has conferred upon mankind.

At the same time with these liberations from damaging and death-dealing infections, however, new and strange circumstances have developed in which men and women must conduct their lives. The ox-cart, the horse and buggy and the bicycle, bad losers in the race for speed, have been crowded out by the motor car. The cry for faster and faster travel has been answered by engines which now permit us to rush along the highways at 50, 60 or 70 miles an hour. Tens of thousands killed annually, and hundreds of thousands injured, measure the consequent jeopardy of life and limb. The meanings of these figures in the distress and remorse of the surviving drivers and their victims, in the pains of the crippled, and in the anguish of inconsolable loss among those who look upon their dead, are wholly immeasurable.

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Accompanying the development of the automobile has been an extraordinary change in the occupation of our people. From a population 60 per cent rural in 1900, we have turned into a population 60 per cent urban. The cities have gained over the farms more than 30 million inhabitants. Whatever its hazards, life in the country has admirable liberty, independence and opportunity for self-direction. Those who have chosen to live in the great cities are often confined to a routine of fixed hours and monotonous tasks. Many lead a sedentary existence, which breaks sharply the age-long racial habit of using the big muscles of the body for gaining sustenance; and the muscles, instead of keeping the body fit, become flabby and inefficient. Furthermore, as hired bookkeepers, clerks and accountants, or as hands in foundries and factories, city dwellers become entangled in the great web of dependency. Specialized work implies limited freedom. The defects of the present commercial and industrial system are not revealed so long as it operates smoothly. It is when a strike among glass molders, for example, stops tens of thousands of other workmen, or the overwhelming of an employer adds the host of his laborers to the masses of the unemployed, that helpless dependence becomes obvious. No wonder that bitter experience can lead to worry and anxiety and to fits of dark depression, and that wives and children must share the gloomy chances with the men who face the tragedy of the lost job. And illness, when it comes, adds its weight to the feeling that support is insecure.

Although reliable statistics are hard to obtain, it would appear that the intense drive and pressure of the new life, its worries and its dreads, place a strain upon men and women which often is too great to be borne. The suicide rate went steadily upward during the recent years of excitement and depression until, in 1932, in the United States it was over 50 per cent higher than during the five years after the War. That rise meant an increase of more than 6000 suicides in 1932 alone. Among diseases suggesting strain are those of the heart and blood vessels, which have nearly trebled in the last three decades. Angina pectoris, emotionally stirred if not emotionally started, now has in New York and Massachusetts three times the number of victims it had in 1900. In New York exophthalmic goiter—that picture of persistent fright—has consistently increased as a cause of death until it has doubled what it was between 1906 and 1910. But these are *mortality* figures, and as such are only indicative of the point which I wish to make. That point is that since the turn of the century an important change in the phenomena of disease has occurred—the seriousness of infection has been undergoing a remarkable decline, and strains and stresses, especially affecting the nervous system, have been on the increase. The disorders resulting therefrom may not lead directly to death and thereby affect statistics, but nevertheless they may cause an immense amount of distress and pain, both directly in the patient himself and indirectly in those bound close by family ties. I refer to the disorders due to emotional causes, fears, resentments and frustrations.

2. *The medical profession has not recognized in a practical way the recent shift in the etiology of disease.* Contemporaneous with the changes which we have just reviewed there has been a development of "healing cults" in our country to a degree not seen in other lands. Persons who have had no discipline whatever in the medical sciences, and no rigorous clinical experience, have been recognized by the public, and to some degree by members of our profession, as capable of undertaking the treatment of the sick. Prominent among these cults are Christian Science and other systems of mental healing. I would add also Freudian methods as practiced by laymen, for Freud himself has argued vigorously in favor of the application of his ideas by psychologists and others who have had no medical training. The Christian Scientists deny the existence of bodily disease altogether and account for so-called illness as being the result of mental error. For the more metaphysical Freudians, likewise, the brain and its modes of government of the organism seem to be quite negligible; the id, the ego, the superego and the censor, and occasional unfortunate family quarrels among these ghostly figures, suffice to explain many of the troubles of existence.

How may this purely mentalistic attitude toward disease be interpreted? The explanation, no doubt, is complex. Fundamentally, I believe, it results from our failure to recognize the considerable rôle which emotional factors have come to play in the onset of illness, especially among people who are harassed by novel and severe demands on their nervous capacities. The medical curriculum has paid relatively little attention to this important matter. In the teaching of medical students emphasis has been laid on disease as it is manifest at the autopsy table or under the microscope. Bacterial agents, poisons, and physical trauma have been recognized as the obvious common causes of disability. In their application, through decades, these notions of pathology have, to be sure, proved their worth. The immense and admirable advances of both curative and preventive medicine during the last four-score of years are properly attributed to them. But perhaps the insistence on morphological pathology and the routine attention to physical signs have led to a belittling and depreciation of human disorders so subtle that they leave no obvious trace.

Is it not true that the recent almost revolutionary transformation of the conditions of life has altered the relative importance of etiological factors? Since bacterial agencies have become less potent, and disturbances of nervous functions have become a greater liability, should not we recognize the change? It will not be easy. Fears and worries, persistent hatred and resentment—what pathology have they? Are they not manifestations of the psyche? And who knows about the psyche? Taught to deal with concrete and demonstrable bodily changes, we are likely to minimize or neglect the influence of an emotional upset, or to call the patient who complains of it "neurotic," perhaps tell him to "go home and forget it," and then be indifferent to the consequences. But emotional upsets have concrete and

demonstrable effects in the organism. It is not to be wondered at, therefore, that when a patient in trouble appeals to us for aid and finds us lacking in sympathy and interest, he turns to faith healers, or Christian Scientists, or psychoanalysts, whether they be expert or not, seeking the help which he needs.

3. *A consideration of the physiological aspects of emotional disturbance discloses a way toward understanding it.* Patients suffering from emotional strain offer to the conventionally trained physician a dilemma; he cannot put his finger on any observable lesion that would yield insight into their troubles, nor can he use his routine methods to explore that complex and mysterious realm where the strain seems to have its center. An escape from this dilemma, which avoids both the demand for palpable evidence of disease and also the vagueness and mysticism of the psychological healers, can be found, I believe, in an examination of the physiological processes which accompany profound emotional experience. As a physiologist I have good reason to regard the movement of nerve impulses along the invisible pathways of the brain as being no more associated with any permanent structural change than one would find, after I cease speaking, in the neurones which now innervate the muscles of my larynx. Yet, in the minute and intricate net of microscopic threads in the cerebral cortex, easy courses may become established which may lead to personal disaster—which may, indeed, result in conduct so intolerable that society will take away from the individual his free action. The habitual pickpocket, the incorrigible forger, the persistent incendiary are persons who exhibit such inwrought and established antisocial behavior. One would look in vain for the pathology of their neurones; yet we must admit that their repeated crimes result from repetition of the same occurrences in their brains. And similarly when typical visceral disturbances occur in regular consequence of emotional excitement—just such disturbances as can be induced by stimulating the visceral nerves—as a physiologist I have good reason to regard them as resulting from discharge of nerve impulses due to the excitement. I propose, therefore, that we try to keep out of the foggy realm of metaphysical medicine and consider emotions from the physiological point of view. Although I shall use words which designate subjective states, such as "fear," "rage" and others, let it be understood that I use them only as convenient abbreviations for activities in the nervous system. Throughout the discussion I shall be concerned with the *physiological* aspects of affective disturbances—that is, with the nervous mechanisms which are involved. Admittedly I am laying little emphasis on the subjective states, the glow of color and warmth, or the darkness of doomsday, with which emotional states may surround simple perceptions or purely intellectual processes. Such states I do not wish to "physiologize." Let us for the present attend to the *expressive* aspect, the "motion" part of the emotion.

From the physiological point of view an emotion is a typical reaction pattern, having in its *expressive* features characteristic facial and postural

attitudes. Only a glance is needed to tell the disposition of a lost child sobbing for his mother, or a young tough who with clenched fist and gritted teeth seeks his enemy, or a thief in wild-eyed flight from an armed policeman. Expressions of grief and rage and fear are ingrained in cerebral structure. Just as sneezing and coughing are reflexes, provided in the congenital organization of the nervous system, so likewise is emotional behavior. One does not have to take lessons in ways of showing one's feelings. Place a man in danger and he is afraid, interfere with him as he satisfies some natural instinct and he becomes angered. When the appropriate stimulus is applied there is commonly a prompt response. So uniform is the response that among different peoples, and even in lower animals, its meaning is understood without explanation; and so persistent is it throughout life that an old man's expression of grief resembles that of a child. In practically all respects the reactions of the body to emotion-provoking situations have the characteristics of simple reflexes.

4. *Profound emotional disturbances are expressed in effects on viscera which are innervated by the autonomic nervous system, and especially by the sympathetic division of that system.* If an emotional reaction is intense, visceral disturbances may occur which involve the entire organism. The movements of the gastrointestinal tract are stopped, the digestive secretions are inhibited, the heart is made to beat more rapidly, the blood pressure is elevated by vasoconstriction in the skin and the splanchnic area, the spleen is contracted so that its content of concentrated corpuscles is squeezed out, the adrenal medulla is made to secrete adrenine, blood sugar is increased by discharge from the liver, and sweat may be poured out on the body surface. All these extensive alterations in the organism are displays of the functioning of the sympathetic division of the autonomic nervous system, whose outreaching filaments are distributed to every region of the body, from the hairs on the top of the head to the glands on the soles of the feet.

There is evidence, also, that intense fear, for example, may involve in addition the parasympathetic control. This effect seems to be more manifest in the activities of the sacral division than in those of the cranial. Emptying of the bladder and rectum and cases of emotional diarrhea at times of excitement belong to this group of responses.

Though there are instances of dominance of the sacral visceral nerves in emotionally disturbing conditions, the typical and more usual effects are those induced by the sympathetic. Simultaneously with the discharge of sympathetic impulses, as already noted, the adrenal medulla is made to secrete. Since the product, adrenine, coöperates with and reinforces sympathetic nerve impulses, we may say that a sympatho-adrenal system provides the means by which, as a rule, emotional states affect the organism.

5. *Emotional stimulation of the sympatho-adrenal system is useful for immediate physical struggle, but otherwise may be deeply disturbing.* The overlapping and interlacing of the preganglionic fibers as they reach up and down the lateral chains of sympathetic ganglia indicate an arrangement for

extensive discharge of nerve impulses throughout the body. The distribution of coöperative adrenine in the blood stream, which is general and indeterminate, supports the view that normally the sympatho-adrenal organization is such as to allow it to work as a whole. When there is intense excitement, that is what happens; the entire organism, as previously mentioned, may be brought under sympatho-adrenal influence, and all the bodily forces mobilized for action. It is noteworthy that the changes wrought under these conditions closely parallel the changes which occur in vigorous muscular effort. Indeed, when we consider the age-long racial association of fear with the impulse to run away or escape, and of anger with the impulse to attack, these bodily changes at critical moments may reasonably be interpreted, as I have detailed elsewhere,[1] as preparations for struggle, perhaps a supreme struggle, for existence.

There is another fundamental function of the sympatho-adrenal system, however, which is related to its emergency function and which must be regarded. That is its service in preserving constant conditions, or homeostasis, in our body fluids, the blood and lymph.[2] Such constancy makes possible for us uniform and consistent performance of our physiological processes. Does the temperature tend to fall and make all our motions slow? The sympathetic constricts blood vessels and increases heat production by discharging adrenine. Does the temperature tend to rise and imperil the integrity of the brain? The sympathetic relaxes surface arteries and pours out sweat for cooling. Is there danger of too little sugar in the blood, with possible convulsions and coma? The sympatho-adrenal agency steps in and liberates a supply of glucose from the hepatic stores and prevents disaster. Does vigorous muscular effort produce non-volatile acid which might overwhelm the alkaline buffer in the blood and stop all action? The sympathetic quickens the pumping of the heart, raises the general blood pressure, makes the blood flow faster through the laboring muscles, unloads extra corpuscles from the spleen, and by thus greatly augmenting the supply of oxygen in the needy parts, permits the non-volatile acid to be burned to innocuous volatile carbon dioxide and the peril is escaped.

The bodily changes in emotional excitement may be considered as anticipatory of many of these dangers. The forces of the organism are put upon a war-footing. But if there is no war to be waged, if the emotion has its natural mobilizing effects on the viscera when there is nothing to be done, obviously the very system which functions to preserve constancy of conditions within us is then employed to upset that constancy. It is not surprising, therefore, that fear and worry and hate can lead to harmful and profoundly disturbing consequences.

6. *The sympatho-adrenal system, though organized for diffuse and widespread action, may influence excessively separate organs or functions.* The evidence for this statement is derived, not from experimental data, but from clinical testimony. To what degree separate organs or functions may be influenced without attendant implication of the rest of the sympathetic has

not been determined. I suggest that here lies an interesting field for research. The indications from case reports point to the possibility that an intense emotional shock, or prolonged emotional strain, may result in one or another of the viscera becoming so subject to sympathetic impulses that even slight perturbations in the daily routine will have noteworthy effects.

Among such conditions may be noted a sensitive reaction of the heart, seen occasionally in soldiers who have been exposed to the terrors of warfare; the slightest excitement sends the pulse bounding up to 140 or 150 beats per minute. Or the vasoconstrictor center is so sensitive that the blood pressure jumps up 40 or 50 millimeters whenever an unhappy event is mentioned. Emotional "dyspepsia" so-called, including disturbances of gastric secretion and motility, due to worry or anger; spasm of the cardiac and pyloric sphincters, readily understandable because both sphincters are tightened by sympathetic impulses; vaginismus, also explained by sympathetic innervation of the encircling smooth muscle—all these are pertinent instances. Perhaps most noteworthy are cases of exophthalmic goiter, in which the striking appearance of the patient is that of chronic fright. The rapid heart, the sweating palms and the bulging eyes all tell a tale of increased activity of at least the upper portion of the sympathetic system. Friedgood's recent studies [3] in the Harvard Physiological Laboratory suggest that sympathetic impulses may act primarily on the anterior lobe of the pituitary and that thyroid involvement is secondary to that. Whatever may be the way in which the disease is evolved, the evidence seems to me overwhelming that a large proportion of the cases have an emotional origin.

7. *The neural basis for emotional expression is organized in the thalamic region of the brain.* The close resemblance between emotional expressions and simple reflexes has already been emphasized. It is characteristic of simple reflexes that they have their centers in the spinal cord or in the part of the brain which is racially most ancient, the primitive brain stem. We have ample evidence to prove that the neurone patterns for the full display of the elementary emotions are organized in this part of the cerebrum. As Bard [4] has shown, the decorticate cat, without any cerebral hemispheres, will snarl and bite when pinched, will crouch and run away when stimulated by a hissing or a loud noise, and will display characteristic mating behavior when appropriately stimulated. Here are the typical signs of rage, fear and sexual excitement, exhibited after the cerebral cortex, which associates the organism with the outer world, has been wholly removed. Characteristically the emotional expression of decorticate animals is extreme. When rage—what we called "sham rage"—occurs in such a truncated creature, the sympathoadrenal system is supremely active; the heart rate may double, blood sugar may increase five-fold, blood pressure is markedly elevated, sweat is poured out on the toe pads, and the hair stands erect from head to tail tip. Because the display of typical emotional responses after decortication tends to be superlative, the inference is obvious that the cortex normally exerts an in-

hibitory influence on the lower centers. Decortication lifts the check and permits the display to have unlimited intensity.

The neural organization demonstrated in lower animals is present also in man. A unilateral tumor in the thalamic region—i.e., at the emotional level—may not alter a voluntary laugh or a voluntary grimace of pain, originated in the cortex. A real laugh or grimace, however, induced by proper affective stimuli, is unilateral. Or a patient with features distorted by one-sided palsy will, when he laughs or weeps because of true feeling, express his attitude with both sides of his face. In short, the muscles of expression are governed from two levels—the cortical level in the cerebral hemispheres, and the emotional level in the diencephalon.

Quite in accord with this evidence are the emotional manifestations in man when he is chemically decorticated. The primary stage of ether anesthesia, and subjection to nitrous oxide, illustrate that condition. Under ether the patient may put up a vigorous fight, and under nitrous oxide he may laugh or weep. In the circumstances voluntary or cortical government has been abolished, but the features of rage or pleasure or grief are still patterned in the emotional level.

Although there is evidence that artificial stimulation of certain parts of the cortex can influence some internal organs, the physiological significance of this fact is still unknown. We do know that as a rule we cannot directly either start or stop the motions of the stomach, for example, or the acceleration of the heart or an extra output of sugar from the liver. Thus, although cortical government may prevail over that part of emotional expression that is seen in features and posture, it is impotent in checking the effects on the viscera. A man apparently calm may be " boiling " inside.

8. *The nervous system is organized in two grand divisions operating outwardly and inwardly.* The universal distribution of the fine nervous filaments to well-nigh every minute area within us need not be emphasized. Stimulation of any point on the skin may send reverberations throughout the whole organism. By means of this intricate and elaborate net of communicating fibers the multitudes of individual parts of the body are unified and made to coöperate.

In the central organization of the nervous system two main divisions may be distinguished. There is what I have called the *exterofective* division, that which by means of sensory receptors is impressed by changes in the outer world and which by means of striated muscles and bony levers works outwardly to change our surroundings and our relation to them. Apart from simple reflexes this division is normally managed from the cerebral cortex. It is related to the external environment, both material and social, in a prodigious complex of impressions, memories, habitual reactions and new adjustments. Through words and pictures, as symbols for objects and acts, the exterofective division may become a part of an indefinitely extensive universe. And then there is the *interofective* division. This is the individual, personal division. It is the autonomic or involuntary system,

already detailed. It works inwardly and affects the muscles and glands of the viscera. It is primarily concerned with the internal environment, the fluid matrix of the body, and, as already noted, normally serves to maintain constancy, or homeostasis, in the watery surroundings of the living parts, inside our dermal envelope. Tendencies toward change—toward hyperthermia or hypothermia, hypoglycemia or acidosis—promptly bring this division into corrective service. In natural circumstances it works cooperatively with the exterofective division, keeping the conditions of the fluid matrix fit for continued activity of that division. But the interofective division is governed at the emotional level. Again, in natural circumstances, this division, under emotional control, coöperates with the exterofective division.

9. *The cerebral cortex serves to interpret the nature of outer objects and to direct emotional forces when these are liberated.* The classical experiments of Pavlov have shown that by means of its agents, the receptors on the body surface, the cerebral cortex analyzes the external environment and brings outer objects into use by the organism. Thus these objects acquire new meaning. A flash of light or the ring of a bell is quite an indifferent stimulus until, for example, it becomes associated with feeding, whereupon it acquires efficacy and is known as a conditioned stimulus. Then the flash or the ring will start the saliva flowing, an effect beyond voluntary control, in the parasympathetic realm. Experiments on man have proved that stimuli can be similarly conditioned which will cause responses, such as narrowing of the pupil and vasoconstriction—again responses beyond voluntary control, and now in the realm of sympathetic innervation. It is evident that, although the viscera are ordinarily not under direct cortical (i.e., voluntary) influence, the natural reflex response can be extended by relating an ineffective with the effective stimulus. In similar manner indifferent objects may be made into effective stimuli for emotional reactions. The banging of a door renews all the horror of a shell-burst and sends the sensitized war-victim into pitiable fright—the noise is only incidental. A visit to a grave brings back acutely the pangs of grief—the grave as such is a bit of elevated earth.

It is by associations, acquired in experience or through verbal symbols, that objects become emotion-provoking. In this category are *words,* words which have been colored by feeling. We have all heard of "fighting words," those derogatory terms which, when earnestly applied to a man, bring anger on the instant. There are also scare-words which, when carelessly applied to a patient, make him anxious and apprehensive. "Your arteries are twisted," "your heart is rather small," or "a little enlarged," "your stomach has sagged," "your blood pressure is high"—these are examples. And then there are comfort-words, expressions which, coming from a trusted physician, banish fear. By use of these symbols the nervous system can be played upon as though an instrument. The charlatan employs

them to establish conditions which he can capitalize for his own profit. The wise doctor knows how to use them as a part of his therapy.

Experimental tests show that emotion-provoking associations of objects and symbols are established in the cerebral cortex. To the decorticate dog the brandished stick is not a menace—it has no meaning. And to the intact dog the stick may mean danger or may mean play, dependent on the way it is used. If in the woods we encounter a bear we shall not be afraid on noting that it is a stuffed bear. We may be very much afraid if it proves to be a live bear and advancing toward us. The total situation is interpreted by cortical processes, and in accord with the interpretation the emotional level discharges into the viscera or not.

If the viscera are roused and the body is prepared for struggle, the cortex once more serves an interpretative function. It directs the response. Bard's decorticate cats, if stimulated by being pinched, showed signs of anger, but they did not react by biting the experimenter; instead they commonly bit their own bodies.[4] Or consider fear of the bear in the woods. Fear is attended by the impulse to escape from danger. But how? Is it better to run or better to climb a tree? Again, in accord with the total situation, cortical operations determine the course to pursue.

10. *The nervous system, the specialized system for integration of the body, is so organized that it may itself disintegrate.* As a rule, when there is a possible antagonism between actions, the nervous controls operate in such a way that the opposed actions are made reciprocal. Thus when we contract the biceps, automatically the antagonistic triceps muscle is relaxed. This mutual adjustment is found universally in the functioning of skeletal muscles which are set to work one against another, and also in smooth muscles which are similarly arranged.

There is a part of the nervous system, however, in which these nice reciprocations may not prevail. That is where the two grand divisions of the system—the exterofective and the interofective—may come into conflict. We have already noted the evidence that the cerebral cortex, governing the exterofective system, exercises a check on the lower centers where the emotional level is found. The cortex provides means whereby emotional responses may be not only conditionally stimulated, but also conditionally inhibited. Thus emotions may be set in opposition to one another. Are we angry and tempted to take vengeance? The cortically associated consequence of punishment by society rouses fear in us, and our action is prevented. Is the soldier, terror-stricken when a shell tears his "buddie" to bits, tempted to desert? If he should, a shooting squad would confront him; the terror is suppressed and he sticks.

These cases illustrate a process which is going on continuously. No doubt in primitive tribes the checks on instinctive behavior are less numerous than in civilized communities. As men have gathered in larger and larger groups, more and more have traditions, codes and laws been imposed to prevent the free display of certain feelings and impulsive acts. Indeed,

the early years of life are characterized by what Myerson [5] has called "the social conditioning of visceral activities." The impulses to defecate and urinate, the powerful sexual impulses, strongly stimulated in our aphrodisiac world, the impulses to avoid dangerous demands upon us and to punish those who have injured us—all these impulses are as natural as breathing, but in civilized society the cortex puts a rein upon them. The emotional or impulsive thalamic level says "act," and the conditioning cortical level says "no," or "circumstances are not appropriate," or "wait awhile." A conflict arises between unconditioned and conditioned impulses. And thus within a system arranged for the unification of the organism, there is antagonism between the portion stimulated to discharge and the portion inhibiting the discharge. And so-called "tensions" develop, because the emotional level, stimulated to discharge but held back from external expression, can have its way *inside the body*. The dog, restrained as he scents his bird, "quivers with excitement," we say. The angry man, withholding his blow, likewise "quivers with excitement." But deeper than these surface showings are the viscera, which the cortex does not control. There the impulsive emotional level, deprived of outward expression, still governs. And the disturbed processes of digestion, the disorderly action of the heart, the fluctuating high pressures in the arteries, the accentuated state of diabetes and the interferences with menstrual function are among the consequences.

The antagonism between nervous activity of the impulsive thalamic level and that of the conditioning and inhibitory cortical level may result in phenomena which the physiologist can explain only by an inferred blocking of neurone pathways. Such blocking might explain the paralysis of the shell-shocked—the so-called "hysterical wound" of the terrified soldier, which resolves his conflict by taking him from danger and also by giving him a reason for his freedom. Such blocking might likewise account for the exclusion of the memory of a painful or disagreeable experience. On the assumption that, by blocking, neurone patterns may become dissociated during antagonistic activities in the brain, we could understand not only isolated "neurograms" of previous events, but their ability to influence, uncontrolled, the interofective apparatus and its visceral effectors. How antagonism between the two grand divisions of the nervous system could result in the assumed dissociation of neurone patterns is quite unknown. The fact of dissociated memories, however, is not questioned.

Conclusion

In the foregoing exposition I have endeavored to show that a highly important change has occurred in the incidence of disease in our country—that serious infections, formerly extensive and disastrous, have markedly decreased or almost disappeared, and that meanwhile conditions involving strain in the nervous system have been greatly augmented. The nervous

system is all-pervasive. It can have effects in remote and secluded portions of the body, far from any obvious lesion. Because it is universal in its effects, disorders which involve the nervous system require consideration of the organism as a whole. But well-nigh all diseases involve the nervous system, because they arouse fears and anxieties and worries, and these feelings are expressed in demonstrable bodily effects.

I have questioned whether we as members of the medical profession have been sufficiently aware of the altered emphasis of illness. Have we not insisted too strongly that only such pathology as can be heard or felt, or tested and measured in the laboratory, is true pathology? Have we not specialized our observations so intently that we do not see the organism because of the organs? Have we not institutionalized medical practice to such a degree that we think more of the disease than we do of the man as an individual and as a member of a social group? An affirmative answer, I believe, should be given to each of these questions.

The cults of mental healers, which have grown to extraordinary proportions, are probably a measure of the failure of the medical profession to consider adequately the rôle of emotion in producing bodily disorders. The practitioners of these cults, in so far as they are untrained laymen, ignorant of the methods of critical diagnosis, are a menace to society. Even if there were no other reason for us to recognize the part which these practitioners undoubtedly play in restoring the morale of the depressed and the anxious, there is the reason that by so recognizing their services and by taking over those services ourselves we should be safeguarding our fellowmen who are ill.

In the course of this discussion I have spoken as a physiologist. The ways in which fears and deep-seated hate and other intense emotional feelings can influence the organism have purposely been described in physiological terms. This was done in order to make clear the point that the bodily effects are as understandable and can be as reasonably explained as clenching the fist or lifting the foot. It was not done because I would neglect the subjective side of impressions and behavior. The organism may be regarded as a "mind-body" unity, and we may quite as appropriately speak of conflicts in the conscious realm as we would speak of opposed impulses in neurones—they may be regarded as different aspects of the same operating system. An attempt to speak of all psychic events in neurological terms is commonly called "neurologizing" or perhaps "physiologizing." But an attempt to designate as "psychic," processes which are demonstrably neural is quite as reprehensibly "psychologizing." If we agree that we are organized as a psycho-organismic unity we need not hesitate to use any convenient terms in mentioning any aspect of behavior or experience, for then we understand that these terms designate one aspect or the other of a living, systematic whole. On that basis we may consider the ways in which success is achieved in the treatment of emotional disorders. Problems of deep feeling may be settled by removing the occasions for them. Sup-

pressed and forgotten fears may be brought into remembrance and abolished by being interpreted. Or rage and hate may be overwhelmed by an inspiring and inclusive love, in the religious sense, which embraces even one's enemies. In all such conversions of turmoil and trouble into serenity and freedom from bodily disturbance, is not the common feature that of resolving conflicts, of bringing harmony where there was discord, of restoring a normal consistency to one's memories and one's attitude and behavior? Perhaps our examination of the physiological antagonism which can develop between the cortex and the thalamic area will reveal to some how internal warfare may profoundly affect the whole organism, and how a return of internal peace may bring miraculously a return of health and happiness. If this excursion into physiology may have that effect, my emotional level would be most pleasantly affected.

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VIRUSES AND THE DISEASES CAUSED BY THEM *

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INFECTIOUS diseases are caused by certain kinds of active agents or their toxins. For convenience, or for other reasons, such agents are divided into the following groups: protozoa, fungi, bacteria, spirochetes, rickettsia, and, finally, the viruses. The viruses and their relation to disease will be the subject of my talk at this time.

The diseases of man that are known to be caused by, or that are strongly suspected of being caused by viruses are measles, German measles, mumps, fever blisters, herpes zoster, varicella, smallpox, vaccinia, rabies, psittacosis, common colds, influenza, St. Louis type of encephalitis, Japanese B type encephalitis, epidemic encephalitis, lymphocytic choriomeningitis, poliomyelitis, lymphogranuloma inguinale, Australian X disease, louping ill, Rift Valley fever, yellow fever, pappataci fever, dengue fever, warts, and molluscum contagiosum.

In addition to man, lower animals, insects, plants, and even bacteria are subject to virus maladies. Foot-and-mouth disease of cattle, hog cholera, canine distemper, sarcomata of chickens, fowl pox, polyhedral diseases of caterpillars, mosaic diseases of plants, and bacteriophagy are examples of virus maladies of hosts other than man. In fact, no form of life seems to be exempt from such diseases. Since much of our knowledge of viruses has come from the study of diseases of hosts other than man, physicians must take them into consideration. Consequently, I shall not apologize for references to work not dealing strictly with diseases of human beings.

Workers in the virus field are frequently confronted with the question, "What is there about viruses that induces investigators to set them apart from ordinary bacteria, protozoa, fungi, spirochetes, and rickettsia?" Such a question implies that all infectious diseases must be caused by agents falling into the well recognized groups just mentioned. Indeed, certain workers are loath to accept the idea that infectious diseases can be caused by active agents possessing a nature different from those already known. In any event, the viruses are smaller than ordinary bacteria, and the size of some, e.g., the viruses of poliomyelitis and foot-and-mouth disease, approximates that of certain protein molecules. Furthermore, the viruses have not been cultivated in vitro in the absence of living susceptible cells, and in that sense they are obligate parasites.

The nature [1] of no virus is definitely known. At present, however, three sets of ideas seem to cover the possibilities: (1) The smallest viruses, e.g., the viruses of foot-and-mouth disease and poliomyelitis, may be inanimate incitants of disease transmissible in series. Stanley [2] believes that the virus of tobacco mosaic is an autocatalytic substance and recently reported that he

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is able regularly to obtain it in crystalline form. His work is significant, and, if his interpretations of it are accepted, progress has been made in regard to the nature of certain viruses. (2) The medium-sized viruses, as exemplified by the etiological agents of yellow fever and fever blisters, may represent forms of life unfamiliar to us. (3) The virus of vaccinia [3, 4, 5] might well be a minute living autonomous organism or a midget in the microbial world, provided the elementary bodies which are infectious and are composed of protein, fats, carbohydrates, and ash represent nothing but individual units of the virus.

That the viruses are exceedingly small and that they have not been shown capable of multiplication in the absence of living cells are not sufficient reasons for considering the variety of diseases caused by them as possessing pathological changes in common. Indeed, one is repeatedly asked, "Why are smallpox, mosaic diseases, poliomyelitis, sarcomata of chickens, and bacteriophagy—diseases with such diverse clinical pictures—grouped together?"

It is now generally agreed that viruses, regardless of their nature, are intimately associated with the cells injured by them. In fact, they are believed to multiply or to be regenerated within such cells. Consequently, it is not surprising that the viruses exert a decided influence upon these parasitized cellular elements.

What effects [6] are produced in cells by the action of viruses? If the action is not too rapid or explosive, and if the affected cells are capable of multiplication, the primary response is hyperplasia resulting in an overgrowth of tissue. In certain diseases this is the chief pathological change, and tumors, such as the sarcomata of fowls and the papillomata of rabbits, are formed. In other maladies, e.g., smallpox and varicella, the primary stimulation with its resulting hyperplasia is followed by a necrosis or destruction of the hyperplastic tissue which causes the formation of characteristic vesicles and pustules. Similar phenomena are also observed in bacteriophagy in which the lysis of the bacteria is preceded by a stimulation of the cells as evidenced by an increased rate of their growth. If the action of the viruses is explosive as in yellow fever and Rift Valley fever, no obvious hyperplasia occurs, and necrosis of cells is the first sign of disease. Finally, if the cells, e.g., nerve cells, attacked by viruses, even though the action of the viruses be slow, are incapable of multiplication, the first sign of infection is lysis or necrobiosis of the cells. Such is the case in poliomyelitis, rabies, and louping ill.

One might ask, "How important a rôle do inclusion bodies and inflammation play in the pathological pictures caused by viruses?" In the past, pathologists devoted most of their attention to these phenomena and considered them of prime importance. It is true that inclusion bodies are of great significance, but they do not occur in all virus maladies. Inflammation is seen in most virus diseases, but it is nothing more than a secondary phenomenon appearing in the wake of cellular destruction. While inclusions are

important and inflammation regularly occurs in virus maladies, hyperplasia, hyperplasia and sequent or accompanying necrosis, and necrosis are the primary pathological phenomena of virus diseases, are common to all, characterize them, and logically permit of their segregation, in spite of their diverse clinical pictures, into the same group of diseases.

Inasmuch as it is obvious that certain viruses induce a marked hyperplasia of tissues, it is easy to understand why such agents are considered in discussions of the cause of cancer. In spite of the great amount of work that has been carried on in this field, the relation of virus tumors to cancer has not been determined.

I have discussed the nature of viruses and the pathological pictures produced by them. Now I shall take up the questions of prevention and treatment of virus maladies. Inasmuch as quarantine measures are of little or no value in the control of this group of diseases, I shall omit a discussion of them and pass immediately to a consideration of prevention and treatment by means of vaccines and convalescent sera, questions of lively interest at the moment, particularly in connection with poliomyelitis.

There seems to be some misunderstanding in regard to the use of the word treatment; some physicians insist that all measures instigated after exposure to an infectious agent, even though the exposed person is still well, constitute treatment, while others are in the habit of employing the word only to designate measures initiated after the onset of signs and symptoms of disease. Consequently, in order to avoid confusion, I shall, in the remainder of my talk which deals with the efficacy of vaccines and immune sera, usually indicate at what time they are administered in relation to exposure and onset of signs of disease.

The principles underlying vaccinations are old and date back to variolation and vaccination against smallpox. In variolation, the infectious agent, introduced into the body in a manner not usually encountered in nature, was supposed to produce a mild disease resulting in immunity. In vaccination, an altered virus in the form of cowpox was used to induce a mild local infection that protected against the severe malady smallpox. These principles actuated Pasteur when he prepared vaccines with an altered but active bacterium or virus. The alteration of the former agent was accidentally accomplished by prolonged cultivation of the organism on an artificial medium, while in the case of the latter agent the change was brought about by repeated passages of rabic virus in rabbits which resulted in "fixed virus." Theobald Smith went one step further and showed that injections of killed bacteria resulted in evidences of immunity in animals receiving them. In spite of the excellent work that has been done, we are still faced with the problem of the proper state of activity of viruses for vaccines and the proper methods of their administration for the prevention of virus maladies.

It is generally conceded that calf lymph is an efficacious means of preventing smallpox, but it appears that this, the oldest and best instrument of

vaccination, can be improved upon in the form of culture vaccine virus administered intradermally.[7]

Fifty years after the introduction of antirabic vaccination, there is no agreement regarding the type of vaccine that should be used. In certain places, the Pasteur type of vaccine is still administered; in others, the Högyes vaccine consisting of freshly prepared active fixed virus is employed; according to the Harris method, repeated injections of dried active fixed virus are given; finally, the Semple vaccine is supposed to contain phenol-inactivated virus.

For the prevention of yellow fever, two vaccines have been employed, one a formalin-inactivated virus,[8] the other an immune serum mixed with a virus altered by repeated passage through mice.[9]

Psittacosis in man is not likely to occur unless the virus enters by way of the upper respiratory tract. In view of this fact, repeated subcutaneous injections of fully active virus have been used for the vaccination of laboratory workers against the disease.[10]

Recently, poliomyelitic virus supposedly inactivated by formalin [11] and virus still active but "attenuated" by sodium ricinoleate [12] have been used for the vaccination of children against infantile paralysis.

Vaccines to be of value must be reasonably safe and in most instances should protect for more than a short period of time. Completely inactivated viruses certainly would be the safest form in which to use them as vaccines for human beings. However, there is no evidence that smallpox and yellow fever can be prevented with vaccines composed of inactive viruses. Furthermore, certain workers are inclined to doubt the value of some batches of Semple vaccine containing inactive rabic virus, because they do not produce protection in dogs against rabies. Indeed, some investigators [13] question whether a serviceable amount of immunity can be produced by a completely inactivated rabic virus, and no one expects a prolonged state of immunity to follow vaccination even with active virus, as is evidenced by the fact that each time a person is bitten by a rabid animal a course of vaccination is given. There is no reliable evidence [14, 15, 16] that either of the recently used vaccines for poliomyelitis is efficacious, while there is grave doubt concerning the safety of one and a certain amount of apprehension in regard to the use of the other.

Why do inactive viruses fail to serve as efficient vaccines? An exact answer to such a question is not available. It may be that some viruses, such as that of poliomyelitis, are very poor antigens even in an active state. Furthermore, the antigenic components [17] of certain viruses may be so labile that they are altered or destroyed in the process of inactivation. Finally, viruses as a rule compose such a minute portion of the tissue emulsions containing them that it is not practical at present to obtain large amounts of them for administration as vaccines.

There is no reason to suppose that the general principles of immunity [18] are not operative in virus diseases. Therefore, inasmuch as it is likely that

most viruses are proteins or are largely composed of proteins, one would expect them to be antigenic and to produce a certain degree of immunity even in an inactive state provided their antigenic properties were not destroyed by inactivation and sufficient amounts were given. In the past, it has not been possible to meet the provisos just mentioned in regard to most of the virus diseases of man. What will happen in the future no one knows.

Vaccines are usually given before exposure, but in the case of smallpox and rabies, vaccinations made after exposure may be efficacious. The incubation period of vaccinia is very short and the rapidly resulting immunity may prevent or modify the activity of the already implanted smallpox virus. The incubation period of rabies is sufficiently long, four weeks or more, to allow the administration of a complete course of vaccination after an individual has been bitten.

The efficacy of vaccines has frequently been estimated in terms of serological tests, and in the case of virus diseases the neutralization test is the one that has usually been employed. Unfortunately the results of neutralization tests made with serum from vaccinated animals may not parallel resistance. This is particularly true in the case of poliomyelitis [19, 20] and rabies,[18] i.e., vaccinated animals may possess neutralizing antibodies and still be susceptible, while others may be resistant in the absence of demonstrable antibodies. Indeed, such a state of affairs may follow an obvious infection with certain viruses. For instance, monkeys that have recovered from a systemic infection with equine encephalomyelitic virus possess neutralizing antibodies in their blood and are systemically resistant to reinfection, but their brains remain entirely susceptible to the action of the virus.[21] Moreover, what takes place in one host as the result of a virus infection may not occur in another, e.g., the brains of monkeys systemically infected with equine encephalomyelitic virus do not become immune, while those of guinea pigs do become resistant under similar circumstances.[21] Furthermore, the events occasioned by the activity of one virus in a host may not parallel those induced by another active agent in the same host as evidenced by the fact that a systemic infection of monkeys with vaccine virus [22] results in an immunity of their central nervous system, while such is not the case, as just pointed out, in regard to a systemic infection with equine encephalomyelitic virus. Consequently, at present the only adequate test for the efficacy of a vaccine is its ability to prevent or modify the disease for which it is given in a specified host.

Before taking up the question of prevention and treatment of virus diseases by means of convalescent or immune sera, I shall describe two sets of experiments that throw considerable light upon the subject.

Several years ago it was shown in my laboratory that typical vaccinal lesions developed in normal rabbit corneas that had been removed from the animals, inoculated with vaccine virus, and cultivated in plasma clots in vitro.[23] It is an interesting fact that pathological lesions typical of this

virus malady can be produced in vitro, and use has been made of it to investigate certain immunological phenomena.[24]

Corneas were removed from normal rabbits and after inoculation with vaccine virus were embedded in plasma clots obtained from rabbits immune to vaccinia. Typical vaccinal lesions with Guarnieri bodies and an abundant amount of active virus developed in such tissues in spite of the fact that in the plasma surrounding them there were sufficient antibodies to fully neutralize the virus. This phenomenon is easily understood in the light of the fact that the activity of vaccine virus can not be materially influenced by immune substances or antibodies once it has made contact with or entered susceptible cells. In this respect our findings are in agreement with those of Rous and Jones[25] who showed that intracellularly situated typhoid bacilli and red blood cells are not susceptible to such injurious agents as potassium cyanide and antisera.

The other set of experiments to which I referred was conducted by Andrewes[26] who showed that antivaccinal serum infiltrated into the shaved skin of a rabbit prevented the development of a vaccinal lesion in the treated skin even though the virus was inoculated immediately afterwards. However, if the virus was injected into the skin five minutes prior to the time that the infiltrations of immune serum were made, no amount of serum sufficed to prevent a lesion, and, if eight hours were allowed to elapse after inoculation, not even the size of the lesion was influenced. Furthermore, it was demonstrated that large amounts of immune serum, administered intravenously shortly after the virus was inoculated intradermally, would prevent a generalized eruption but would exert no influence upon the lesion at the site of the inoculation. In this connection, it should be remembered that as a rule no evidence of infection is seen during the first 48 hours after vaccine virus is injected into the skin of a rabbit.

The results of the above experiments clearly indicate that once a virus has entered a cell its activity can not be influenced by large amounts of antiviral serum. Furthermore, such findings aid one in interpreting the results obtained in the use of immune sera for the prevention and treatment of virus diseases in man.

Convalescent measles serum given to a child just before and within six days after exposure to measles usually prevents the appearance of evidences of the disease; serum administered between the sixth and tenth days after exposure as a rule modifies the severity of the infection; serum given after the onset of signs of infection, which most frequently appear on the tenth day, is according to observant and critical workers without beneficial effects.

In attempts to interpret the significance of the results just described, let us assume that the virus of measles enters the upper respiratory tract and multiplies in some part not definitely determined. Beginning with the sixth day after exposure the virus is distributed from the primary focus to different parts of the body by way of the blood stream, and, from the course of events, it is not unreasonable to suppose that by the tenth day sufficient

virus has been distributed for the infection of most of the cells susceptible at that particular time in any given individual. If our assumptions are correct, serum administered during the first six days after exposure should not necessarily inhibit the multiplication of virus in the primary focus but should prevent its distribution and the development of illness and evidences of measles. Moreover, serum given between the sixth and tenth days should prevent the distribution of that part of the virus that has not already been distributed or should hinder its entry into susceptible cells not already involved, and, in view of this fact, should modify the severity of the infection but not prevent it. Finally, serum administered after the tenth day should not be beneficial, because most if not all the cells that are to be affected have by that time already been entered by the virus.

Those who are familiar with measles will say, "But the rash comes on the fourteenth instead of the tenth day." That is true. Viruses, however, may be in cells several days before evidences of the fact become obvious. Furthermore, according to some observers, a measles rash can be made evident by means of ultraviolet light 24 to 48 hours before it is detectable under ordinary conditions.

In the case of measles, many assumptions have been made regarding the location of the virus in the body at different times during the course of the infection. Unfortunately, a good experimental animal is not yet available for the testing of some of the assumptions. In the case of certain virus diseases of the central nervous system, however, there are suitable experimental animals from which accurate data have been obtained regarding the location and concentration of the viruses from the time that they are instilled into the nose until the animals die.

Fite and Webster [27] have shown that after instillation of louping ill virus into the nose of mice the active agent is present in the brain four days before the animals evidence signs of illness.

Galloway and Perdrau [28] found that after instillation of louping ill virus into the nose of monkeys the active agent was well distributed throughout the central nervous system several days before the animals showed signs of sickness.

Hurst [21] instilled equine encephalomyelitic virus into the nose of monkeys, sacrificed them at different times after inoculation, tested various parts of their central nervous systems for the presence of the virus, and correlated his findings with clinical observations made on the monkeys before they were killed. According to him, all parts of the central nervous system except the cord contained virus within 30 hours after the onset of fever, and several hours later, at the time of the onset of nervous symptoms, even the lumbar cord was infectious.

Webster and Clow [29] dropped the virus of the St. Louis type of encephalitis into the nose of mice, sacrificed some at different times in order to test for the presence of virus in various parts of the brain and cord, killed others to determine the time of appearance and progression of lesions, and

allowed others to sicken and die in order to determine the time of onset of clinical signs and symptoms. The data obtained in this manner clearly showed that virus was present in the tissues 24 to 48 hours before the appearance of lesions detectable under the microscope, and that all parts of the brain and cord contained large amounts of virus before the animals became ill.

Faber and Gebhardt [30] conducted similar experiments with monkeys that had been infected by means of intranasal instillation of poliomyelitic virus. Their findings indicate that by the fifth, sixth, or seventh day after inoculation, at which time only an occasional rise of temperature or tremor and hyperesthesia were present and before paralysis had occurred, virus was distributed throughout the central nervous system.

In view of the above mentioned results obtained by a number of workers by means of many experiments with different viruses in different hosts, it seems logical to assume that the virus of poliomyelitis by the time signs and symptoms of disease become obvious in infected human beings has already reached practically all of the nerve cells that are likely to be attacked. If such be the case, then one would expect convalescent serum given after the onset of signs of the disease to be valueless. Indeed, such expectations are in accord with the clinical findings reported by careful workers who have used the serum for therapeutic purposes under properly controlled conditions both in monkeys and in human beings.

If the factors described above as being responsible for the therapeutic failures of convalescent poliomyelitic serum are not operative in every case, there are others that enhance the likelihood that failures will regularly occur, such as the inability of antibodies to penetrate the blood-brain barrier and reach the virus in the tissues of the brain and cord. Furthermore, it is highly improbable that antibodies in potent antisera placed in the subarachnoid space are capable of reaching virus situated in the depths of the brain and cord, because drainage from the subarachnoid space is as a rule not back into the central nervous system but into the general circulation.

In the first part of the talk, I discussed problems relating to the nature of viruses and the character of lesions produced by them, while in the latter section I dealt with matters pertaining to the prevention and treatment of virus diseases by means of vaccines and convalescent or immune sera. I have presented data of a general rather than a concrete nature in the hope of initiating a train of thought that will lead to a greater appreciation of problems in the virus field and a better understanding of phenomena daily encountered in the practice of medicine.

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THROMBOPENIC PURPURA; AN ANALYSIS OF 160 CASES *

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The present concept of thrombopenic purpura as a definite syndrome has gradually been evolved and separated from the maze of hemorrhagic diseases. In the earliest fragmentary descriptions of purpura it was noted in association with the pestilent fevers,[1] later it was found apart from these, and still more recently was separated as a distinct entity. A proper understanding of the condition, however, awaited the discovery of the blood platelets by Donne and Arnold [2] and the observation by Denys [3] and Hayem [5] that the platelets were diminished in certain cases of purpura. This feature was subsequently verified by numerous observers and forms the basis for the syndrome which is characterized by (1) a diminished number of platelets, (2) prolonged bleeding time but an essentially normal coagulation time, (3) a non-retractile clot, and (4) a positive constrictor or arm band test. A simple classification which is similar to that of Pratt [7] and Rosenthal [8] is as follows:

I. Idiopathic Thrombopenic Purpura
   (1) Acute
   (2) Chronic
II. Secondary Thrombopenic Purpura
   (1) Infections
   (2) Toxins and drugs
   (3) Blood dyscrasias
   (4) Diseases of the liver
   (5) Miscellaneous

There are many reports of hereditary hemorrhagic diseases in the literature, and among these are some cases which present the clinical and laboratory features of thrombopenic purpura.[9, 10, 11] Although these do not constitute a large group, they occur with sufficient frequency so that an hereditary type of thrombopenic purpura must be acknowledged.

Since many conditions may lead to the clinical manifestations of purpura without the characteristic hematological features, and especially without a reduction of the platelets, the universal recognition of thrombopenic purpura as a distinct syndrome has been delayed, and there has been much confusion in the literature. The early classifications of purpura were based purely on the clinical features, and this has been continued in spite of more recent and improved methods of blood examination. The criteria given above for the diagnosis of thrombopenic purpura eliminate from this discussion the simple purpuras so common in youth and senility, the anaphylactoid purpura with

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abdominal and joint manifestations (Henoch-Schönlein), the purpuras due to avitaminosis (scurvy) as well as those cases of purpura associated with vascular changes which occur with many acute infections and intoxications.

Idiopathic Thrombopenic Purpura

The pathogenesis of idiopathic thrombopenic purpura has given rise to much discussion [12] and cannot be considered as definitely settled. That the platelets originate from the megakaryocytes in the bone marrow,[13] have a life of but a few days,[14] and are destroyed by the spleen, is quite generally accepted. They accelerate coagulation,[2] improve the degree of syneresis,[15] and perhaps play some part in combating infections and in the production of anaphylactic reactions. Their rôle in thrombopenic purpura is not clear, and some deny the existence of this syndrome as separate from those forms of purpura in which the clinical manifestations are similar, but in which the platelets are present in normal numbers.[16] If we accept the syndrome as possible of recognition we must consider the cause of the platelet deficiency to determine whether it results from under-production of platelets, as originally proposed by Frank,[17] or from their over-destruction by the spleen.[18] We may further consider the possibilities of the actual loss of platelets through hemorrhage, the formation of defective platelets which are removed by the spleen, or the removal of platelets from the circulation in an attempt to control the capillary hemorrhage. For a further discussion of the cause and the effects of this reduction in the number of platelets the reader is referred to the work of Mackay,[2] Lescher and Hubble,[19] and De Sanctis and Allen.[20] The most generally accepted theory is that a deficiency in platelets is the primary feature of the condition and that bone marrow insufficiency is responsible for this deficiency. The possibility has been advanced, however, that there are two types of thrombopenic purpura, as yet indistinguishable by clinical means, one of which is due to deficient or faulty production of platelets while the second results from their increased destruction by the spleen.

The close association of thrombopenic purpura, aplastic anemia and agranulocytosis and the similarity of many of their features have been emphasized. The three diseases have been grouped together under the term "marrow insufficiency." [21, 22] Their occurrence under similar conditions, their frequent association and the origin of each of the cell types within the bone marrow give credence to this correlation and, in certain cases, cause difficulty in the differential diagnosis. Although presenting distinct and separate clinical features in most instances, there are certain borderline cases with an overlapping of the hematological pictures, as might be expected when the histogenesis of the various cell types is considered.

The histologic changes in the bone marrow and spleen are varied and have tended to confuse rather than clarify our concept of the pathogenesis. Studies of the bone marrow have not been numerous in cases of idiopathic thrombopenic purpura, and in those in which they have been made, the find-

ings are divergent. Those cases in which the megakaryocytes are diminished in number or possess shrunken and pyknotic nuclei lend support to Frank's theory.[17] In other cases with an equally low platelet count, the megakaryocytes of the bone marrow are present in normal numbers and show no morphologic changes.[23, 24] This group tends to support Kaznelson's theory [18] that the bone marrow is not the seat of the primary disorder. Lawrence and Knutti [24] studied the bone marrow of six patients; four of these showed no abnormalities and two had a diminished number of megakaryocytes. They suggest, as did Lescher and Hubble,[19] that in those patients with normal bone marrow the primary lesion is in the spleen with a resultant increased destruction of normally formed platelets, and that these are the patients who show improvement after splenectomy. It is interesting to note that experimental production of thrombopenic purpura by means of antiplatelet serum has led to equally divergent histological findings in the bone marrow.[25]

Certain cases show hyperplasia of the marrow,[26] either diffuse or patchy, as a regenerative response to repeated hemorrhages. All the elements of the marrow may take part in the hyperplasia, even the megakaryocytes.

Examination of the spleen reveals no uniformity in the histologic picture, so that the findings are not specific or diagnostic. In many instances the spleen is essentially normal, and in others, as in two of those removed in this clinic, there is a simple fibrosis. In many instances the spleen is enlarged and presents endothelial cell hyperplasia of both the sinuses and Malpighian corpuscles.[27] The lymphoid elements may be diminished, normal, or increased, and the platelets within the spleen may be increased or entirely absent.[2] Thickening of the arterial walls in the vessels to the follicles has been noted in some instances.

With such a diverse histologic picture in both spleen and bone marrow, one can but conclude that there is no uniform pathological change and at present can but speculate as to the possibility of two distinct types of idiopathic thrombopenic purpura.

Secondary Thrombopenic Purpura

An enormous number of case reports have appeared in the literature showing the association of thrombopenic purpura with a wide variety of primary disorders and intoxications. One can find no feature present in all cases to explain the diminution in platelets so that the pathogenesis is just as obscure as in the idiopathic form. In certain instances definite bone marrow pathology is present to account for the thrombopenia while in others a chemical or bacterial toxin which either destroys the platelets or inhibits their production has been hypothesized. The bone marrow may be fatty or aplastic in cases of marrow insufficiency, it may be hyperplastic with an overgrowth of myeloid or lymphatic elements in leukemia, or may show no essential histologic change in cases of infection or intoxication.

The hyperplasia of aleukemic myelosis may be found in a biopsy of the sternum or a lymph node [28] so that this procedure is worthy of consideration in obscure cases.

Clinical Features

The clinical features are the same in both the idiopathic and secondary types. The diagnosis of thrombopenic purpura must rest on the laboratory findings of prolonged bleeding time, positive constrictor test, non-retractile clot and lowered blood platelets rather than on the clinical picture. Hemorrhage into the skin, either as purpuric spots or as ecchymoses, is the most characteristic feature, the former frequently appearing spontaneously with successive crops of innumerable small hemorrhages on the extremities, neck and upper trunk, while the latter may occur as a result of a very minor trauma. These skin manifestations are not uniformly present and their absence may forestall the correct diagnosis. Many patients have hemorrhages from the mucous membranes of the nose, mouth, gastrointestinal or genito-urinary tracts without involvement of the skin. Profuse uterine hemorrhage is a frequent manifestation of this syndrome in women, and hemoptysis, hematuria, and cerebral hemorrhage are not uncommon. These hemorrhagic manifestations are so frequently present without skin involvement that thrombopenic purpura must be considered in all cases of unexplained hemorrhage. In many of the cases which are secondary to other disease there are no hemorrhagic manifestations, and the diagnosis is made purely on the laboratory data found on routine hematological examination. In other instances the hemorrhagic features overshadow the primary condition. In the idiopathic variety, which is more common in females and usually appears early in life, there is frequently a history of having bled or bruised easily since birth.

The blood picture in the idiopathic cases is that of a post-hemorrhagic anemia, and although certain morphological changes in the platelets have been described,[29] they are not constant enough for diagnostic purposes. The reduction in the number of platelets varies, but Minot [22] has given 60,000 per cu. mm. as the critical level below which hemorrhage is apt to occur. We have used the thrombocytocrit method of Van Allen [30] for platelet determinations, since in our hands it has been more reliable for routine use than platelet counts.

Complete hematological studies have been done in 160 cases of thrombopenic purpura. Of these, 17 were found to be of the idiopathic type, and 143 were secondary thrombopenic purpura. The further subdivision of these groups is best shown in the following tabulation. The subgroups will then be discussed separately.

Analysis of Cases

I.	Idiopathic Thrombopenic Purpura	17
	(1) Acute	3
	(2) Chronic	14

II.	Secondary Thrombopenic Purpura		143
	(1) Infection	25	
	(2) Toxins and drugs	6	
	(3) Blood dyscrasias	81	
	Lymphatic leukemia		18
	Lymphoma		11
	Myelogenous leukemia		15
	Aleukemic myelosis		7
	Acute (stem cell) leukemia		1
	Pernicious anemia		14
	Aplastic anemia		11
	Familial hemolytic icterus		1
	Acquired hemolytic icterus		1
	Anemia of pregnancy		1
	Idiopathic hypochromic anemia		1
	(4) Liver disease	12	
	(5) Miscellaneous	19	

Secondary Thrombopenic Purpura

Blood Dyscrasias

Leukemia. Under the heading secondary thrombopenic purpura the largest group, 81 cases, was associated with disease of the hematopoietic system, and of these leukemia was the most frequent. There were 18 cases associated with lymphatic leukemia, in four of which it appeared as a terminal event in the chronic, slowly progressing form in adults. The other 14 cases occurred in association with the more acute rapidly progressing lymphatic leukemia of childhood, nine of which were in the subleukemic state described by Abt [31] and Hyland.[32] There were 15 cases of myelogenous leukemia complicated by thrombopenic purpura. In the early stage of myelogenous leukemia the platelets are not infrequently increased in number, so that the complication occurred as a terminal event in the chronic cases but appeared early in the course of the acute forms. Thrombopenic purpura was present in each of the seven cases of aleukemic myelosis which we have studied, and the resultant hemorrhagic tendencies were the predominant feature of the illness. One case of acute blast cell leukemia was accompanied by this syndrome. It is apparent that thrombopenic purpura is most apt to appear in the acute rapidly progressing forms of leukemia, but may occur as a terminal event in the more chronic forms. It very definitely adds to the gravity of the prognosis inasmuch as it signifies a more rapid course. In some instances the hemorrhagic features are the most striking part of the clinical picture, giving rise to difficulties in diagnosis, especially in the aleukemic forms in which the blood picture is not diagnostic. Examination of the bone marrow either by biopsy or sternal puncture may be necessary for a correct interpretation.

Lymphoma. Thrombopenic purpura was a less frequent complication in the other forms of lymphoma than was true of lymphatic leukemia. Eleven cases were found, four of which occurred with the sclerosing type (Hodgkin's disease) and seven with the lymphoblastic and lymphocytic type without leukemia. Although not a common causative agent, these diseases

must be considered as possibilities when thrombopenic purpura appears, even though splenomegaly and lymphadenopathy are not prominent. The presence of this complication adds to the gravity of the prognosis, since it appears more commonly in the rapidly progressing forms or as a terminal feature in the chronic cases.

Pernicious Anemia. In 14 patients thrombopenic purpura was found associated with pernicious anemia, a much lower incidence than with leukemia. In none of these patients were the hemorrhagic features of purpura clinically apparent except for a tendency to bruise more easily than normal or to bleed more readily from slight trauma, and the syndrome was discovered only by routine blood examinations. A reduction in the platelet count is a characteristic feature of pernicious anemia, and it is surprising that thrombopenic purpura does not occur more frequently with this disease. This complication did not influence the course nor the prognosis of pernicious anemia, and with an induced remission the platelets returned to a normal level. One case of thrombopenic purpura was found in each of the following conditions, in none of which did it produce any clinical manifestations: acquired hemolytic icterus, familial hemolytic icterus, idiopathic hypochromic anemia and anemia of pregnancy.

Aplastic Anemia. There were 11 cases of idiopathic aplastic anemia, seven adults and four children, in which thrombopenic purpura was present. The clinical manifestations of purpura were present in all but one of these cases, and frequently were the predominant feature. The diagnosis of aplastic anemia was verified by necropsy in three of the patients who died in the hospital. There were certain borderline cases in which it was difficult to differentiate between idiopathic thrombopenic purpura and aplastic anemia, but in all of the above cases the anemia seemed to be the primary feature, appearing before the hemorrhagic features rather than being dependent on the loss of blood. The association of the two conditions is almost constant in the late stages of aplastic anemia, and the severe hemorrhages hasten the end in most instances.

Liver Disease

Various forms of liver disease are well recognized as a cause of thrombopenic purpura, and 12 such instances were encountered in this series. The mechanism by which the platelets are affected is not known although with the seat of fibrinogen formation in the liver, it is not surprising to find changes in blood coagulation and syneresis. The clinical features of purpura were prominent in only one of these patients, and spontaneous hemorrhages did not appear in the others in spite of the presence of laboratory features of the syndrome. The appearance of the complication, regardless of the severity of its manifestations, adversely affected the prognosis. In this group there were seven cases of Banti's syndrome, one of which was syphilitic in origin, four cases of portal cirrhosis and one of syphilis of the liver.

Toxins and Drugs

A review of the literature reveals that thrombopenic purpura is frequently the result of the administration of various drugs, and cases have been reported after arsphenamine,[33] bismarsen,[34] gold,[35] quinine,[36] bismuth,[37] and iodine.[38] In the present series only six similar instances were found. Three appeared with the administration of arsenic, two followed the application of organic hair dye, and one was associated with chronic benzol poisoning. In all of this group the associated anemia was severe and of the aplastic type.

Miscellaneous

Among the miscellaneous diseases there were many entirely unrelated conditions giving rise to this complication. Included in the group were four cases of carcinoma, two of the breast and one each of the stomach and pancreas. Three of these had given rise to widespread metastasis with bone involvement, while the one arising in the pancreas had no demonstrable metastatic lesions. There was one case of extramedullary myeloblastoma without evident bone involvement and one case of melanosarcoma. One patient with myxedema presented this syndrome, as did one with Graves' disease who had not received iodine. There was one case of chronic glomerulo-nephritis. A roentgen-ray technician developed the typical laboratory features of this syndrome together with a mild degree of anemia, although there were no hemorrhagic manifestations. With greater precautions against exposure to roentgen-rays the blood returned to normal A patient with xeroderma pigmentosum developed the typical features of aplastic anemia, agranulocytosis and thrombopenic purpura, with severe hemorrhages from the nose, mouth and gastrointestinal tract. At autopsy, however, no aplasia of the sternal or rib marrow was apparent.

There were eight cases on whom no additional information was available so that the primary lesion, if any, is unknown. No cases were found in which an allergic reaction was responsible for the thrombopenia, although such cases are numerous in the literature and it has been demonstrated that the administration of an allergen to a susceptible individual produces a distinct drop in the platelet count.[39]

Infection

The importance of infection as an etiological agent in secondary thrombopenic purpura has been repeatedly emphasized, and the eradication of foci is recognized as an essential feature in the treatment of the idiopathic cases. In many instances it is difficult to evaluate with certainty the rôle which infection plays in the etiology. In the present series there were 25 patients in whom it was felt that infection was undoubtedly the cause. Only six of these occurred in adults, two of whom had subacute bacterial endocarditis and one had broncho-pneumonia. One male, aged 27, had repeated attacks of gonorrheal urethritis with a subsequent arthritis and prostatitis. Epi-

sodes of purpura and hemorrhage appeared with the acute exacerbations of urethritis, and in addition to the characteristic findings of thrombopenic purpura there was a modern anemia and agranulocytosis. At necropsy there was no evidence of aplasia of the bone marrow. In one patient, a female aged 34, severe nasal, gingival and uterine hemorrhages, together with an extensive purpuric eruption, followed immediately an acute upper respiratory infection. On admission to the hospital the specific laboratory features of thrombopenic purpura were present, and the gums were so swollen and bloody as to suggest leukemic infiltration. Biopsy of both gums and bone marrow presented a normal histologic picture. One year later the blood was normal in every respect and there had been no recurrence of the hemorrhagic features. Another girl, aged 17, had repeated episodes of purpuric eruption for four years and more recently had two severe episodes of hemorrhage. The first appearance of purpura was immediately after diphtheria so that it was difficult to determine whether the infection was the primary etiological factor or whether the infection merely precipitated the onset in a patient with potential or latent idiopathic thrombopenic purpura.

Infection as an etiological agent plays a more important rôle in children than in adults, and 19 cases secondary to infection were found in patients under 14 years of age. In one child miliary tuberculosis not only caused the typical laboratory and clinical features of thrombopenic purpura but also a differential blood picture almost indistinguishable from lymphatic leukemia. Necropsy examination revealed a generalized miliary tuberculosis with involvement of the bone marrow. Tuberculosis appears in the literature as a frequent causative agent and has even been suggested as the responsible agent in most cases of the idiopathic form.[40] One typical example of thrombopenic purpura with severe hemorrhages occurred during the course of epidemic parotitis and one during an acute infectious enteritis. Three cases were associated with septicemia, a condition which is prone to produce not only this syndrome but also an aplastic anemia, and it is difficult at times to determine whether the septicemia was the primary factor or occurred as a terminal event. There were five cases which appeared in association with measles, either during the period of eruption or during convalescence. Acute upper respiratory infections were most common in producing this syndrome in children, and there were eight cases in which the ears, tonsils or sinuses were involved. It is more commonly associated with an acute infection but occurs also with chronic forms. Acute exacerbations of the infection may cause recurrent attacks of hemorrhage as in one six year old boy who had repeated hemorrhagic episodes over a period of a year, each accompanying an acute exacerbation of otitis media. In none of the cases secondary to infection which we have been able to follow has there been a recurrence of symptoms after eradication of the infection. This propensity of infection to cause thrombopenic purpura supports the

contention that all obvious foci should be removed even in those patients with an apparently idiopathic form.

Idiopathic Thrombopenic Purpura

The diagnosis of idiopathic thrombopenic purpura must rest not only on the presence of the characteristic laboratory and clinical manifestations, but also on the rigid exclusion of all diseases which may cause the secondary form. Certain cases, especially in elderly patients with no preceding evidences of hemorrhage, are undoubtedly considered as idiopathic only because of our inability to locate the primary trouble. Remissions can be induced by blood transfusion in the majority of idiopathic cases and should be done as a diagnostic as well as therapeutic measure before more radical procedures are undertaken. In the acute fulminating type, which is frequently fatal in spite of blood transfusions, splenectomy is usually of no avail so that the delay for diagnostic purposes is justifiable.

Seventeen cases in this series were considered to be idiopathic in origin, nine occurring in adults and eight in children under 14 years of age. Among the adult cases, one, a female aged 24, was acutely fatal, the first episode of hemorrhage being uncontrollable by any means at our disposal. One male, aged 38, had bruised easily for many years but had no hemorrhages or purpuric spots until two years before admission to the hospital. The bleeding at this time was easily controlled by transfusion, and further therapeutic procedures were postponed so as to determine the subsequent course. There have been no recurrences as yet. One male, aged 50, had recurrent hemorrhages for 38 years, and two other elderly patients gave histories of intermittent hemorrhages and purpura of many years' duration. The same history of recurrent hemorrhages and purpura was obtained in the younger adults, so that in all cases the actual onset of symptoms was in childhood or early adult life. Splenectomy was not performed in any of this group.

The ages of the children with idiopathic thrombopenic purpura ranged from four to 14 years and were equally divided between males and females. Two of these eight cases were of the acute type. One of these died of cerebral hemorrhage soon after admission. The bleeding was controlled in the other acute case, she returned home and in the subsequent 12 months has had no recurrence except a mild epistaxis during the course of measles. The remaining six cases were of the chronic type and gave histories of hemorrhage or of bruising easily for from one to several years, and in one instance, in a boy of six, these features had been noted by the parents since birth. One chronic case, on which a splenectomy was advised, but was refused by the parents, died after returning home. Transfusions were given to all patients in this group to control the hemorrhage, and the immediate response was good in all instances except one case that died of cerebral hemorrhage. Foci of infection were eradicated when present and splenec-

tomy was performed on three patients. Two of these three patients were subsequently followed and there has been complete disappearance of symptoms. The histologic picture in one spleen was normal while the other two showed only simple fibrosis. Two of the patients who did not have a splenectomy have had no recurrence of symptoms in the year which has elapsed since they were discharged from the hospital.

Treatment

The treatment of secondary thrombopenic purpura depends entirely upon the primary condition, and in those cases in which this can be eliminated the purpuric manifestations disappear. The prognosis in those cases associated with infections, pernicious anemia and other conditions responding to therapy, is good whereas little can be accomplished in the others. For immediate control of the hemorrhage transfusion of whole blood is indicated, either intramuscularly, or preferably intravenously. This is effective in many instances although in those with acute leukemia, aleukemic myelosis and aplastic anemia, it usually has but little effect. Various coagulants and hemostatics have been tried but are of little avail, and we have found no case in which these were entirely successful. Since splenectomy is acutely fatal in many of these cases and of no avail in the others, the necessity of an accurate diagnosis cannot be stressed too strongly.

There is no universal agreement as to the proper treatment of the idiopathic form of thrombopenic purpura. Since infections play so prominent a rôle in the production of the secondary forms as well as precipitating attacks in the idiopathic variety, they should be eradicated when present regardless of whether they are definitely related to the symptoms or not. Special diets,[41] high vitamin intake and calcium salts have been advocated but a specific effect has not been definitely proved. Antivenin [42] has been used with some success and snake venom has been recommended for its temporary hemostatic effect.[43, 44] Peptone shock therapy has been advocated [45] and we have experienced some success in certain hemorrhagic diseases by sensitizing the patient to horse serum and then producing an anaphylactic reaction. The use of roentgen-rays over the spleen has been found to be of only temporary value [46] and ligation of the splenic artery has been proposed but not generally accepted.

Splenectomy should be considered in the idiopathic form only when the diagnosis has been established with absolute certainty. Many of these cases tend to improve spontaneously with advancing age, and the symptoms may completely or almost completely disappear in adult life so that removal of the spleen is unnecessary. In other cases the hemorrhage is not sufficient to warrant splenectomy, even at the onset of the illness. Since remissions can be induced in practically all cases of idiopathic thrombopenic purpura by means of transfusion, it is best to watch the patient through one or more attacks to determine the severity and frequency of the hemorrhages. If

they are severe and show no evidence of diminishing intensity, the spleen should be removed during a quiescent period. The operation carries a high mortality in the acute stages so that it is justifiable to attempt to carry the patient through this stage by transfusions. Splenectomy may produce a complete cure, an amelioration of symptoms, or the condition may recur with equal severity. At the present time there is no definite criterion on which to base the prognosis following splenectomy, although it is hoped that sternal biopsy or puncture may eventually give this information. The operation is best withheld until it has been determined whether the attacks are becoming more severe, until the effects of transfusion have been noted and until the effectiveness of eradication of focal infections has been determined. Spence,[27] in recording the results of splenectomy in 101 cases, found good results in 90.9 per cent of the chronic and 16.6 per cent of the acute cases. Whipple [47] collected 81 cases and found 6 deaths among 73 chronic cases and 7 deaths in 8 acute cases. Sixty-one patients were followed postoperatively and 51 had good results, 4 were fairly successful and 6 were not relieved. It has been repeatedly emphasized that protection against infections is an extremely important feature in the postoperative care of the patient.

Summary

One hundred and sixty cases of thrombopenic purpura have been studied with respect to the etiology, prognosis and treatment. It was found that 143 of these cases were of the secondary type.

The importance of infection in the etiology of secondary thrombopenic purpura and its significance as a precipitating factor in the idiopathic cases have been emphasized.

The diagnostic difficulties have been mentioned, and the importance of an accurate diagnosis and of a proper period of observation prior to splenectomy in all cases is stressed.

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THE THERAPEUTIC EFFECT OF SOLUTION OF POTASSIUM ARSENITE IN CHRONIC MYELOGENOUS LEUKEMIA *

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For many years roentgen therapy has been the most satisfactory method of treatment of the chronic leukemias. It is generally agreed that life is not materially prolonged by irradiation, but in favorable cases symptomatic and hematologic improvement occurs for variable periods of time. Some patients experience uncomfortable reactions to treatment, others become refractory to irradiation, and occasionally an alarming depression of the red and white blood cells occurs. In the absence of specific forms of therapy for the disease, there is need of other palliative measures which may be used in place of, or in conjunction with, roentgen therapy. Interest in the use of solution of potassium arsenite was revived in 1931 by the reports of Forkner and Scott.[1, 2] These authors observed striking symptomatic and hematologic improvement in nine of ten cases of chronic myelogenous leukemia, treated for short periods of time with toxic or subtoxic doses of solution of potassium arsenite (Fowler's solution). During the past three years several reports discussing the treatment of leukemia have contained brief mention of arsenic as one of the useful drugs in the treatment of chronic myelogenous leukemia, but detailed confirmation of these observations has not appeared in the available literature.

Material for this report consists of seven patients with chronic myelogenous leukemia treated with one or more prolonged courses of solution of potassium arsenite, and observed for periods of from several months to three years. In five patients, arsenic therapy has been supplemented by roentgen treatments. In general our conclusions confirm and amplify those of Forkner and Scott.

Except for short periods of observation in the hospital, patients were followed either in the office or the Out-Patient Department, where frequent clinical and hematologic observations were made. Differential blood counts were made in films prepared on cover slips, stained with Wright-Giemsa stain. Schilling's classification of the leukocytes was used. In the figures both the myelocyte and the juvenile of this classification are included as "myelocytes." Solution of potassium arsenite was given in rapidly increasing doses until toxic symptoms appeared; subsequent dosage was regulated as necessary to maintain a subtoxic level of the drug. Iron, when given, was prescribed in the form of 12 Blaud's pills or six grams of ferric

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ammonium citrate daily. Roentgen-ray treatments, as indicated in roentgen units, were given over the spleen or chest. The course of each patient will be discussed briefly in relation to an accompanying chart, in which changes in the hemoglobin, the red and white blood cell counts and the differential counts are shown. Non-essential details are omitted from the case reports.

Case Reports

Case 1. D. S., a 58 year old salesman, was admitted to the Strong Memorial Hospital on February 2, 1934. During the previous six months he had noted fatigue, shortness of breath on exertion and loss of 15 lbs. in weight. For about one month before admission to the hospital there had been intermittent abdominal pain, weakness, anorexia and pallor. Two weeks previously his physician had found a white blood cell count of 167,000, had made a diagnosis of leukemia and prescribed Fowler's solution in doses of 10 drops three times daily. The development of conjunctivitis of the right eye prompted his admission to the hospital.

In 1931 a diagnosis of coronary occlusion had been made. This was followed by thrombophlebitis in the right leg, which incapacitated him for a period of about six months. A white blood cell count of 16,000 was noted during this illness.

On examination the patient appeared chronically ill, was pale and apparently had lost weight recently. He had an acute catarrhal conjunctivitis on the right. There were several small retinal hemorrhages. The edge of the spleen was palpable 8 centimeters below the costal margin. The liver edge was felt 8 centimeters below the costal margin and was tender. There was a moderate degree of benign prostatic hypertrophy.

Laboratory findings: Blood hemoglobin 6.4 gm. per 100 c.c., red blood cells 1,990,000 per cu. mm., white blood cells 193,000 per cu. mm. The differential leukocyte formula was as follows: eosinophiles, 1 per cent; myeloblasts, 1.5 per cent; myelocytes, 37 per cent; juveniles, 2 per cent; stab neutrophiles, 2.5 per cent; segment neutrophiles, 52.5 per cent; lymphocytes, 1.5 per cent. Platelets were abundant. Blood non-protein nitrogen was 61 mg. per cent; uric acid, 4.76 mg. per cent; serum albumin, 4.72 gm. per cent; serum globulin, 2.2 gm. per cent; creatinine, 2.6 mg. per cent. Basal metabolic rate was plus 31 per cent. The urine showed a small amount of albumin, an occasional granular cast and red blood cell. The electrocardiograph showed left axis deviation, without other abnormalities.

The conjunctivitis subsided within a few days. During February three doses of deep roentgen-ray therapy were given over the spleen and chest. A moderate drop in the total leukocyte count occurred but there was no change in the percentage of immature cells and no clinical improvement. Shortly after admission to the hospital the patient developed difficulty in urination, presumably due to prostatic obstruction. On February 21, the blood non-protein nitrogen was 92 mg. per cent; creatinine, 6.2 mg. per cent; uric acid, 8.7 mg. per cent. Detailed studies of kidney function were not done because of the precarious condition of the patient.

On March 7, two weeks after the last roentgen-ray treatment, weakness, fatigue and dyspnea had increased, the total leukocyte count had risen to the previous level and the anemia had become more severe. No change had occurred in the size of the spleen or liver. The urinary symptoms had disappeared, but the non-protein nitrogen was 75 mg. per cent; creatinine, 5.3 mg. per cent; uric acid, 7.8 mg. per cent. At this time the administration of Fowler's solution was begun.

On April 13, arsenic was discontinued because of nausea and vomiting, which subsided within a few days. At this time the leukocyte count was 15,200 per cubic millimeter, of which only 9 per cent were immature cells. The strength and appetite had improved, and he had gained weight during the period of arsenic therapy. There

had been some decrease in the size of the spleen. There had been no urinary symptoms, and urinalysis showed no abnormalities. On April 23, the blood non-protein nitrogen was 48 mg. per cent, uric acid, 4.0 mg. per cent. An increase in the reticulocytes, which reached 12 per cent, was followed by striking improvement in the anemia. The administration of iron in the form of 12 Blaud's pills per day was begun on April 26, and he received a blood transfusion on May 2. It should be noted that the reticulocyte response and the increase in hemoglobin and red blood cells occurred before the institution of the latter procedures.

In May, because of return of the leukocyte count and percentage of immature cells to a high level, the administration of Fowler's solution was resumed. Clinical improvement continued, he gained further weight, and there was no significant change in the level of blood non-protein nitrogen or uric acid. There was again a gradual decrease in the total white blood cell count to a value but little above normal. The decrease in percentage of immature cells was less striking. In July, Fowler's solution was again discontinued because of weakness, anorexia and diarrhea. These symptoms disappeared within a few days. There had been little change in the size of the spleen. Without therapy the leukocyte count rose again and remained high. In spite of a moderate degree of anemia, he felt quite well, without undue fatigue or weakness, during the next four months. Treatment was omitted during this period because of the satisfactory clinical condition.

In December he was again admitted to the hospital with fever and respiratory difficulty of a few days' duration. There were signs of pneumonia of the lower lobe of the left lung. The spleen was somewhat larger than it had been previously. At this time the blood non-protein nitrogen was 110 mg. per cent; uric acid, 10.7 mg. per cent; creatinine, 5.0 mg. per cent. The patient died, apparently as the result of pneumonia, a few hours after admission to the hospital.

The autopsy findings were characteristic of chronic myeloid leukemia. All bone marrow sections showed marked myeloid hyperplasia. There were extensive myeloid infiltrations in the spleen, which weighed 2175 grams, in the liver, which weighed 3800 grams, and in the kidneys. Bronchopneumonia was present in both lungs. Canalization of an old thrombus in the right femoral vein had occurred. There was nothing to indicate that the typical pathologic picture of chronic myelogenous leukemia had been altered by the previous arsenic therapy.

Case 2. M. V., a 24 year old housewife, was first seen in the Out-Patient Department October 23, 1933 complaining of abdominal pain of an indefinite nature. During the previous year she had lost about 15 pounds in weight. For about two months she had noted "weakness of the eyes" and had been unable to read or sew. There had been some fatigue on exertion but no limitation of activity.

Examination showed moderate pallor, no glandular enlargement. Ophthalmoscopic examination revealed bilateral papilledema. The retinal veins were engorged and tortuous, of irregular caliber; in some areas they were barely visible. There were several old retinal hemorrhages. The spleen was enlarged, extending to the right of the umbilicus with its lower border palpable 22 cm. below the costal margin.

Blood hemoglobin was 8.9 gm. per 100 c.c.; red blood cells, 2,750,000 per cu. mm.; white blood cells, 322,000 per cu. mm. Differential formula was as follows: basophiles, 1.5 per cent; eosinophiles, 2 per cent; myelocytes, 46.5 per cent; juveniles, 8 per cent; stab neutrophiles, 18.5 per cent; segment neutrophiles, 22 per cent; lymphocytes, 1.5 per cent. One nucleated red blood cell per 100 leukocytes was found. Platelets were abundant.

Within two weeks after starting Fowler's solution the eyes had improved, strength had returned and the abdominal discomfort had diminished. There was gradual decrease in the total leukocyte count and percentage of immature cells. The anemia improved. The spleen gradually became smaller and in May 1934 could not

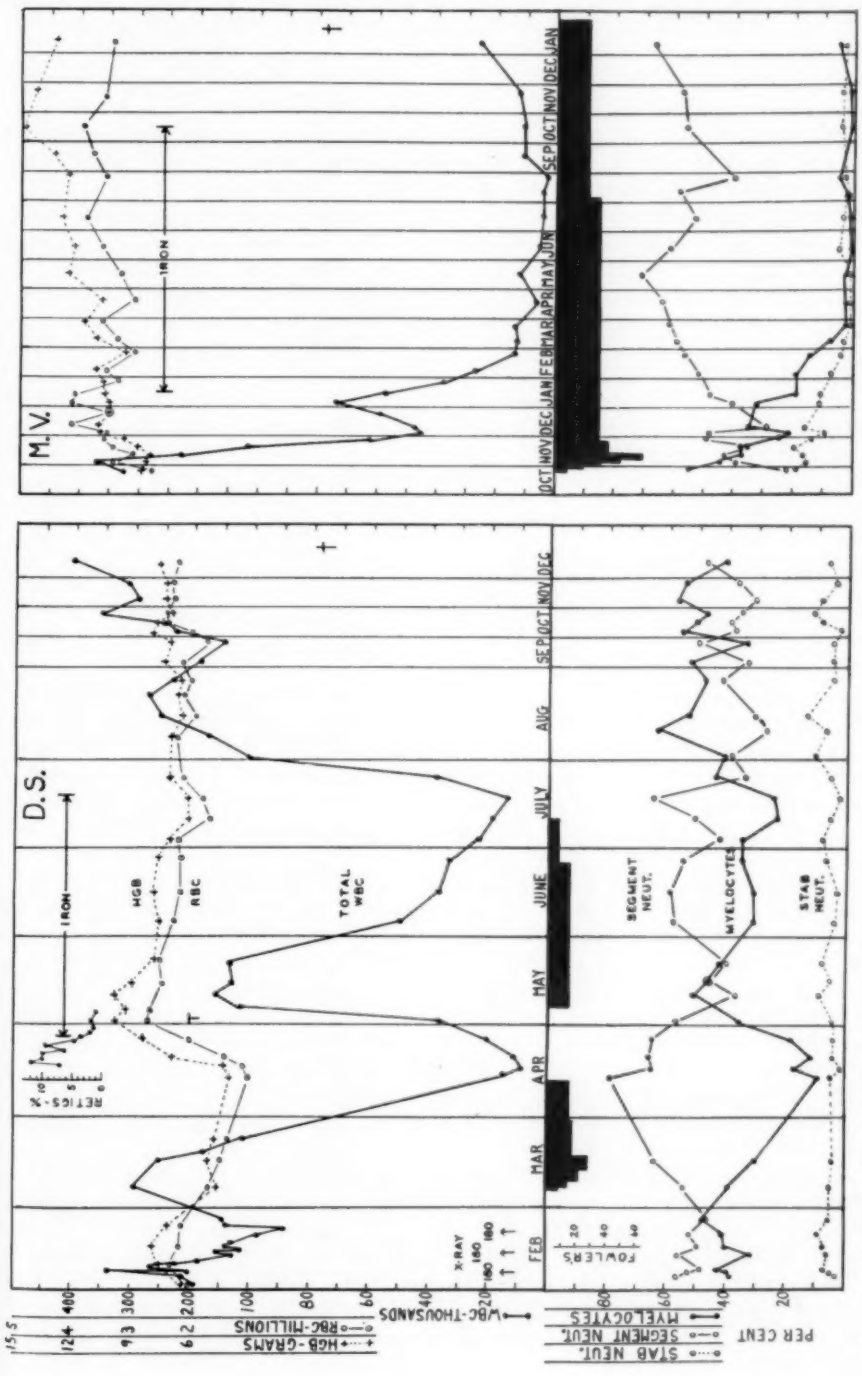

FIG. 1. Case 1 (D. S.), and Case 2 (M. V.). The daily dose of solution of potassium arsenite is indicated in drops per day. Roentgen treatments are indicated by arrows, with the dose in roentgen units. T indicates transfusion.

be felt. The eyegrounds became normal in appearance and remained so. From February 1934 until the time of her death, almost a year later, the patient was without symptoms except those attributed to mild arsenic intoxication, which occurred from time to time. For a period of 10 months before death the leukocyte count was within, or slightly above normal limits and the immature cells remained below 5 per cent. During the period of arsenic therapy, which was continued in subtoxic doses without interruption for 15 months, a diffuse, tan colored pigmentation with some dryness of the skin appeared and persisted over the entire body.

During the latter part of January, the patient died at home, of pneumonia, after an acute illness of three days' duration. Autopsy was not done.

Case 3. J. L., a 54 year old retired miller, was admitted to the Strong Memorial Hospital December 29, 1932 complaining of weakness and fever. He had suffered from fatigue and general malaise for about six months. For the past six weeks he had been weak, tired and " feverish." He had had drenching night sweats, anorexia, dyspnea on slight exertion and had lost 25 pounds in weight.

On examination, the temperature was 39° C. He appeared chronically ill and had evidently lost weight. There were small soft lymph glands in each axilla. There were small hemorrhages in each ocular fundus and one small petechial hemorrhage in the left buccal mucosa. The spleen extended six centimeters below the costal margin.

Blood hemoglobin was 10.5 gm. per 100 c.c., red blood cell count was 3,700,000 per cu. mm.; white blood cell count was 91,600 per cu. mm. The differential leukocyte formula was as follows: basophiles, 2 per cent; eosinophiles, 4 per cent; myelocytes, 30 per cent; juveniles, 12.5 per cent; stab neutrophiles, 11.5 per cent; segment neutrophiles, 35 per cent; lymphocytes, 4 per cent. Platelets were present in normal numbers.

Two doses of deep roentgen-ray therapy, totalling 350 roentgen units given over the spleen, resulted in a marked reduction in the total leukocyte count and in the percentage of immature cells. There was gradual clinical improvement, with increase in strength and disappearance of fever. Additional roentgen-ray therapy was given in January and February. In February 1933, the administration of Fowler's solution was begun and was followed by further improvement. In March the spleen was barely palpable. The patient returned to work and remained symptom free for several months.

In September 1933 while still taking Fowler's solution, fatigue, weakness, chills and fever, and splenomegaly returned. A single roentgen treatment was followed by disappearance of the above symptoms for several months. In October, toxic symptoms necessitated reduction of the dose of Fowler's solution, which was finally discontinued in January 1934. During the next four months the patient received four roentgen-ray treatments because of weakness, fatigue, fever and increase in the leukocyte count and immature cells. Each treatment was followed by temporary improvement in symptoms and in the white blood cell picture. The anemia became progressively more severe. A temporary rise in red blood cells and hemoglobin followed a transfusion early in May 1934. The patient died at home early in June 1934. Autopsy was not done.

Case 4. E. G., a 51 year old housewife, was admitted to the Strong Memorial Hospital on January 22, 1935. For about 18 months she had noted increasing fatigue, slight pallor and some dyspnea on exertion. Five weeks before admission to the hospital there had been an acute illness characterized by fever, malaise, sore throat and non-productive cough. During this illness her physician found a white blood cell count of 80,000 and made a diagnosis of leukemia. A single dose of roentgen-ray therapy had been given, followed by reduction in the white blood cell count to 41,000. Fowler's solution was prescribed in doses of 15 drops daily. During the last few days before admission to the hospital an itching eruption had appeared in both inguinal regions.

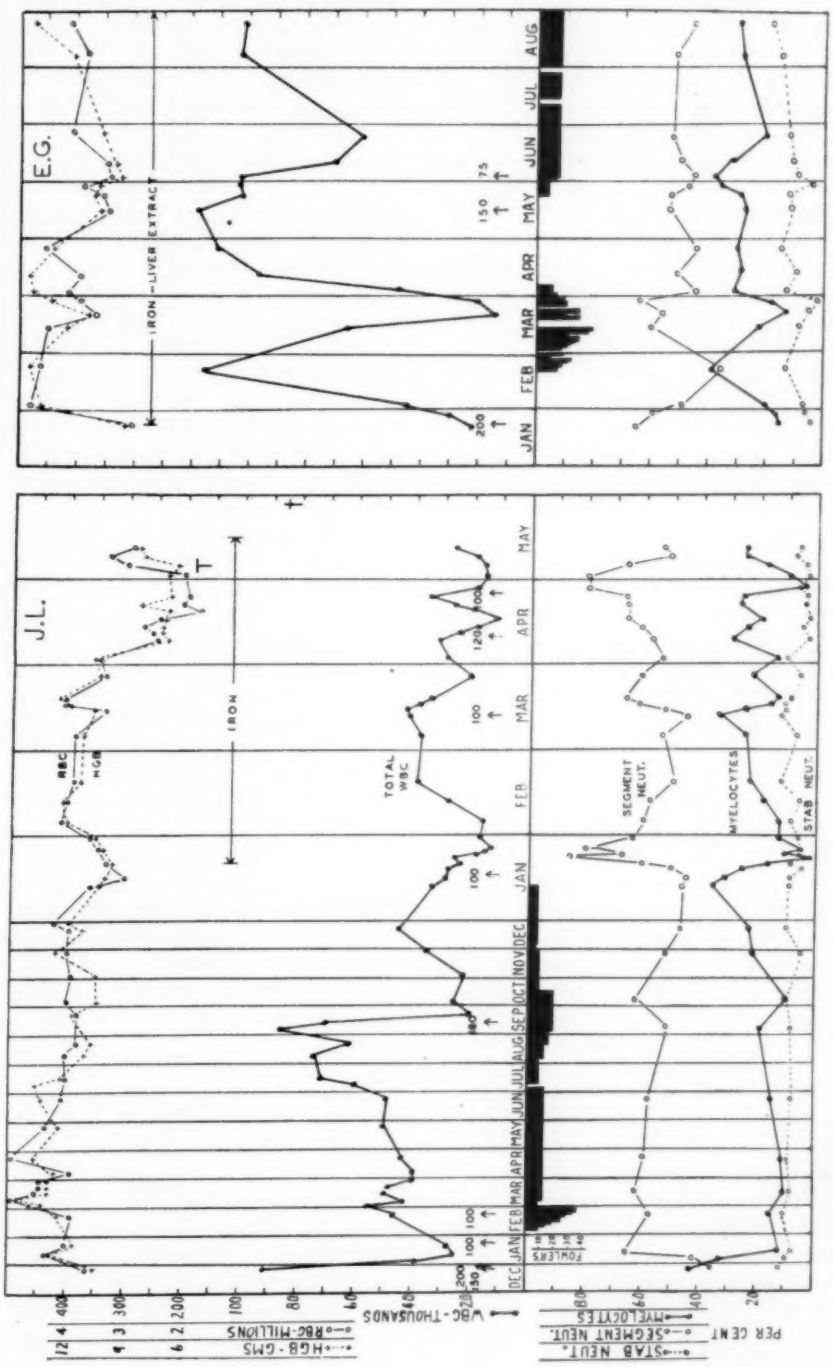

FIG. 2. Case 3 (J. L.), and Case 4 (E. G.). The daily dose of solution of potassium arsenite is indicated in drops per day. Roentgen treatments are indicated by arrows, with the dose in roentgen units. T indicates transfusion.

Physical examination showed a maculo-papular, erythematous eruption in the right axilla, in the pubic and inguinal regions, and over the labia majora. The edge of the spleen was palpable under the costal margin.

Blood hemoglobin was 9.75 gm. per 100 c.c.; red blood cells 3,090,000 per cu. mm., white blood cells 22,900 per cu. mm. The differential leukocyte count was as follows: basophiles, 3 per cent, eosinophiles, 8 per cent; myelocytes, 7.5 per cent; juveniles, 7.5 per cent; stab neutrophiles, 6 per cent; segment neutrophiles 59.5 per cent; lymphocytes, 4.5 per cent. Platelets were plentiful.

A single dose of roentgen-ray therapy was given over the perineal and suprapubic regions. It was thought at the time that the skin lesions might be a form of leukemia cutis. Subsequent observations, however, indicated that the eruption was an arsenic dermatitis and that the blood picture had been favorably influenced by the previous arsenic therapy. Iron and Lilly's liver extract No. 55 were prescribed. During the following month, the skin lesions completely cleared but weakness and fatigue continued and the total leukocyte count and percentage of immature cells increased. The administration of Fowler's solution resulted in a striking diminution in the number of leukocytes and percentage of immature cells; fatigue and weakness were markedly improved. However, symptoms of arsenic toxicity appeared, and were accompanied by an itching skin eruption similar in character and location to that previously observed. This became so bothersome that Fowler's solution had to be discontinued; two weeks later the skin lesions had disappeared.

Without arsenic, the leukocyte count rose rapidly, the percentage of immature cells increased, the anemia again became more severe, and fatigue and weakness returned. A single dose of roentgen-ray therapy in May resulted in a severe reaction with prostration, increased weakness, anorexia, nausea and vomiting for several days. A smaller dose of roentgen-ray therapy two weeks later resulted in a similar but less marked reaction. The administration of Fowler's solution was again started on May 20 and continued in subtoxic amounts. Although the changes in the white blood cell picture were not striking, symptomatic relief was experienced, and improvement in the anemia was noted. At the time of writing, the clinical condition is satisfactory and the spleen is not palpable, although the total white blood cell count and the percentage of immature cells are quite high.

Case 5. N. E., a 20 year old unmarried waitress, was admitted to the Rochester Municipal Hospital September 30, 1932, with a history of chronic fatigue and loss of 20 pounds in weight during the previous year. For two days before admission there had been sharp, cramplike pains in the abdomen, without other symptoms.

Examination showed a chronically ill young woman, who appeared pale and tired. There were several ecchymoses over the legs. The spleen was markedly enlarged, extending to the right beyond the mid-line and downward to the iliac crest. A leathery friction rub was heard over the splenic area.

At the time of admission blood hemoglobin was 7.5 gm. per 100 c.c., red blood cells, 2,720,000 per cu. mm., white blood cells 439,000 per cu. mm. Differential count was as follows: basophiles, 3.5 per cent; eosinophiles, 1 per cent; myeloblasts, 1 per cent; myelocytes, 38 per cent; juveniles, 14 per cent; stab neutrophiles, 15 per cent; segment neutrophiles, 24.5 per cent; lymphocytes, 2 per cent; degenerated cells, 1 per cent. Two nucleated red blood cells were seen in counting 100 white blood cells. Platelets were abundant. Basal metabolic rate was plus 30 per cent.

The administration of Fowler's solution in increasing amounts was begun on October 2 and continued for six weeks in subtoxic doses, with occasional rest periods because of toxic symptoms. During the latter part of October there was a sharp decrease in the total white blood cell count, accompanied by a decrease in immature cells and followed by an increase in the red blood cell count and hemoglobin. These changes were accompanied by marked symptomatic improvement, disappearance of the abdominal discomfort and splenic friction rub, and diminution in size of the spleen.

On November 18, 1932 the patient was discharged to her physician in a neighboring state. She received one roentgen-ray treatment during the second week in December. When last seen on January 20, 1933 she was symptomatically well and there had been further improvement in the anemia. The total leukocyte count, however, had risen to 160,000. The further course of this patient is not known.

Case 6. M. T., a 50 year old housewife, was admitted to the Strong Memorial Hospital on March 21, 1934 complaining of a mass in the abdomen. During the preceding year she had noted increasing fatigue and backache, palpitation and dyspnea on exertion and left-sided abdominal enlargement. During the past six months there had been loss of 35 pounds in weight and a chronic non-productive cough. For two months before admission there had been occasional skin hemorrhages without antecedent trauma.

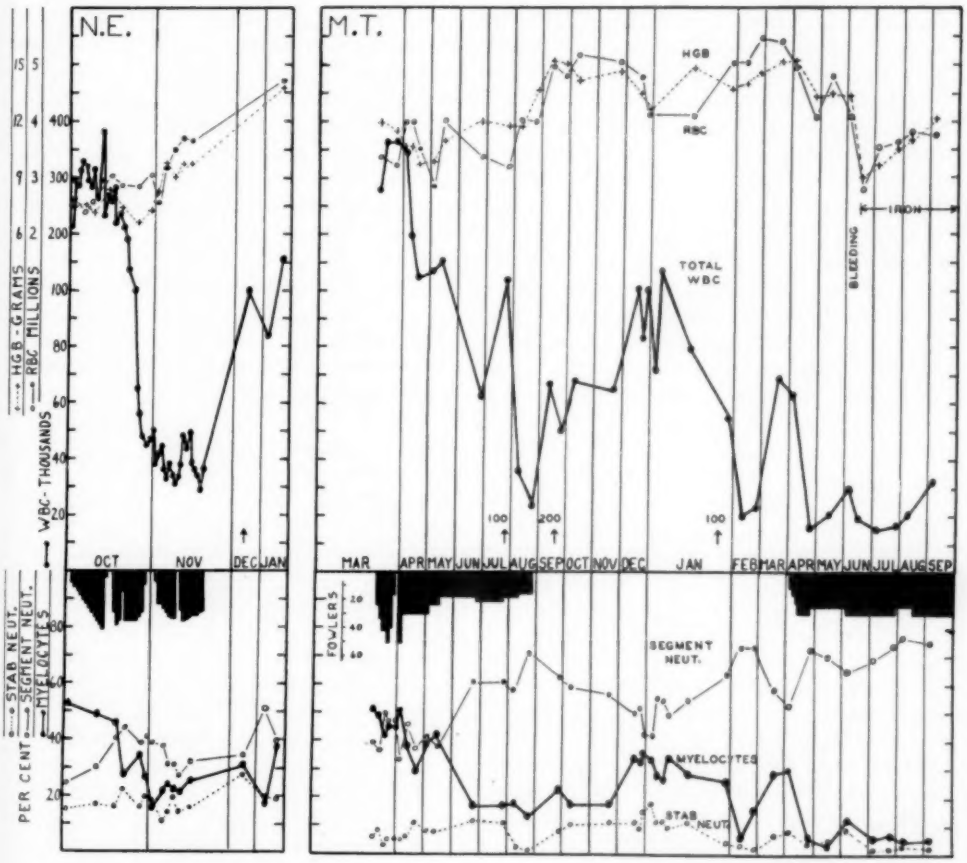

FIG. 3. Case 5 (N. E.), and Case 6 (M. T.). The daily dose of solution of potassium arsenite is indicated in drops per day. Roentgen treatments are indicated by arrows, with the dose in roentgen units.

The patient was an obese woman, appearing chronically ill. The spleen extended to the right beyond the midline and downward to the iliac crest.

Blood hemoglobin was 12 gm. per 100 c.c., red blood cells numbered 3,800,000 per cu. mm., white blood cells, 275,000 per cu. mm. Differential leukocyte formula was as follows: eosinophiles, 3 per cent; myelocytes, 40 per cent; juveniles, 11 per

cent; stab neutrophiles, 6 per cent; segmented neutrophiles, 39 per cent; lymphocytes, 1 per cent. Platelets were abundant. Basal metabolic rate was plus 57 per cent.

Fowler's solution was administered in subtoxic doses during the next five and a half months. During this time there was a moderate decrease in the total leukocyte count and in the percentage of immature neutrophiles. The patient gained in weight and strength, the respiratory symptoms disappeared, the spleen decreased in size and the eyegrounds cleared. In July, 100 roentgen units of roentgen-ray therapy were administered to the lateral splenic and thoracic areas; this was followed by an increase in the red blood cells and hemoglobin and by further reduction in the white blood cell count. During the latter part of August, Fowler's solution was discontinued because of generalized itching and an exfoliative eruption in the pubic region. Within three weeks the skin lesions had cleared. A single roentgen-ray treatment in September apparently did not influence the blood picture. In January 1935 the third roentgen-ray treatment was given because of fatigue and weakness. This was followed by symptomatic improvement and by a sharp but temporary reduction in the total leukocyte count and the percentage of immature cells.

In April 1935, the administration of Fowler's solution resulted in a precipitous decrease in the total leukocyte count and in the percentage of immature cells. Since that time strength and endurance have remained good and the white blood cell count and the percentage of myelocytes in the peripheral blood have been relatively low. However, the spleen, which could not be felt in April, gradually increased in size. When last seen, in September, the edge of the spleen was palpable 10 cm. below the costal margin, in spite of the favorable blood picture.

In June 1935, tooth extraction was followed by profuse hemorrhage for a period of about 10 days. Blood smears taken before and during the bleeding showed an abundance of platelets. The bleeding was finally controlled by a pressure splint, but resulted in a marked increase in the degree of anemia. This patient also has had occasional episodes of vaginal bleeding, controlled by gynecological measures. The bleeding time and coagulation time have been normal. There has been no apparent correlation of the pelvic bleeding with fluctuations in the blood picture.

Case 7. J. N., a 36 year old farmer, was admitted to the Strong Memorial Hospital September 9, 1932 complaining of pain in the abdomen. There had been increasing weakness for the past 20 months. For several weeks he had noted anorexia, fatigue, dyspnea on exertion and loss of 20 pounds in weight. During the three days previous to admission there had been sharp pain in the upper left abdominal quadrant aggravated by cough, deep breathing, and changes in position.

Examination showed an appearance of chronic illness, pallor, small lymph nodes in the cervical and inguinal regions. There were numerous fresh and old retinal hemorrhages. The spleen was enlarged, with the lower border extending downward to the level of the umbilicus. A friction rub was audible over the splenic area.

Blood hemoglobin was 8.6 gm. per 100 c.c., red blood cells numbered 2,660,000 per cu. mm., white blood cells 176,000 per cu. mm. The differential leukocyte formula was as follows: eosinophiles, 1.5 per cent; myeloblasts, 2 per cent; myelocytes, 43 per cent; juveniles, 21 per cent; stab neutrophiles, 8 per cent; segment neutrophiles, 21 per cent; lymphocytes, 2.5 per cent. Platelets were present in approximately normal numbers. Basal metabolic rate was plus 29 per cent.

The administration of subtoxic doses of Fowler's solution resulted in a striking diminution in the number of leukocytes and in the percentage of immature cells, but both increased rapidly when the administration of arsenic was discontinued (figure 4). The administration of Fowler's solution in amounts as large as could be tolerated again resulted in striking hematologic improvement which persisted for about three weeks after discontinuing the drug. The leukocyte count was reduced to a normal value and immature cells almost entirely disappeared from the peripheral circulation. Meanwhile there had been steady clinical improvement. Symptoms present on ad-

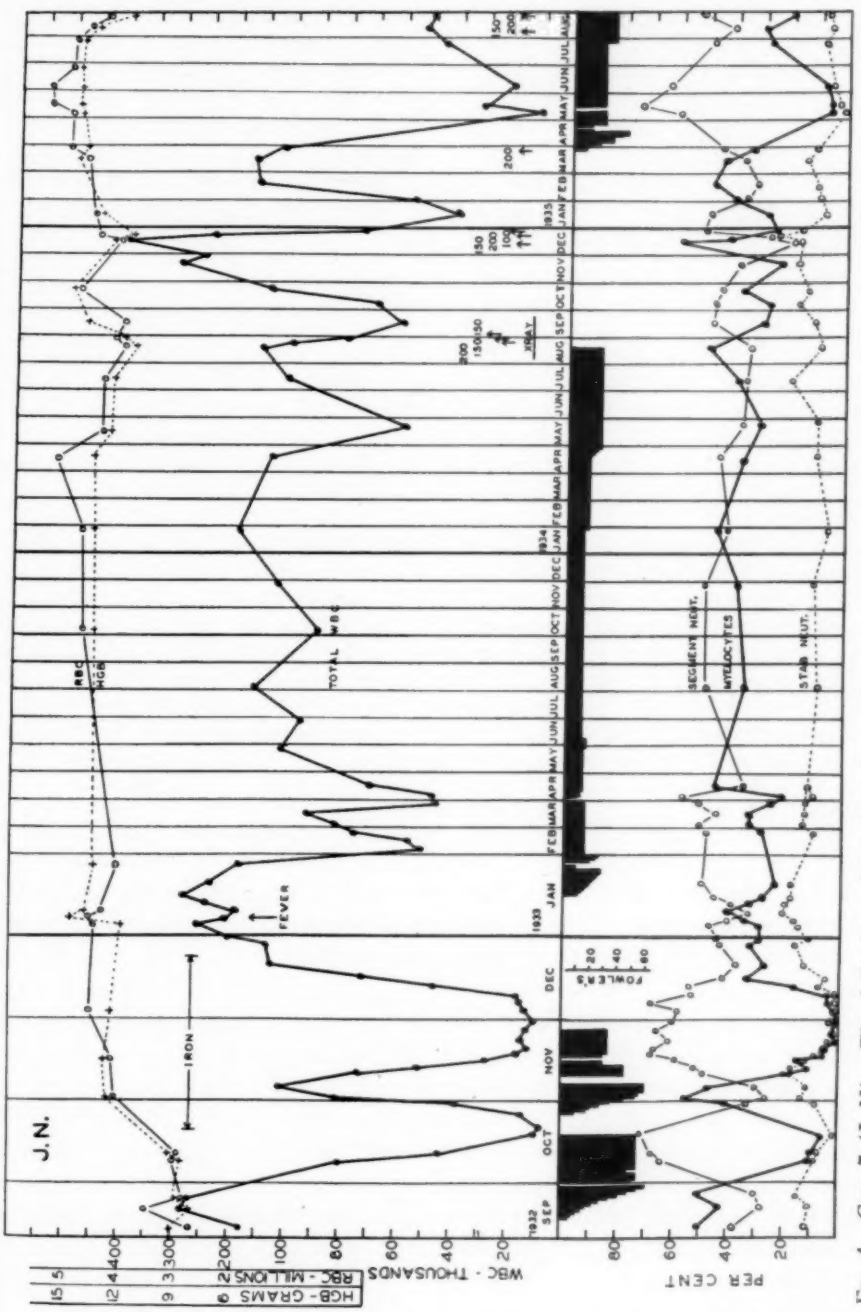

FIG. 4. Case 7 (J. N.). The daily dose of solution of potassium arsenite is indicated in drops per day. Roentgen treatments are indicated by arrows, with the dose in roentgen units.

mission disappeared. The patient gained 20 pounds in weight and returned to work. In December 1932, the spleen was palpable under the costal margin.

Without therapy the total leukocyte count and the percentage of immature cells rapidly increased. On January 6, 1933, the patient submitted to 4 hours of artificial fever at a temperature of 40.5 to 41.0° C. as an experimental procedure. Except for a temporary increase in hemoglobin, there was no significant change in the hematologic or clinical picture.

On January 15, 1933, the administration of Fowler's solution was again begun and was continued in subtoxic doses without interruption for 19 months. During this period the total leukocyte count and the percentage of immature cells remained relatively high. However, a satisfactory red blood cell and hemoglobin level was maintained, the splenic edge remained at the costal margin, the patient worked regularly as a laborer and was symptom-free except for intermittent, mild manifestations of arsenic toxicity.

During the month of August 1934, there was rapid increase in the size of the spleen to the level of the umbilicus and return of fatigue and weakness, shortness of breath and abdominal fullness. Arsenic was temporarily discontinued. During the next six months two courses of roentgen-ray therapy were given over the spleen. Each of these resulted in temporary clinical improvement, slight reduction in the size of the spleen, and a moderate decrease in the total leukocyte count and the number of immature cells.

In April 1935, the administration of Fowler's solution was again resumed and resulted in striking hematologic and clinical improvement. He again became symptom-free and was able to return to work regularly as a laborer in a gravel pit. The spleen was reduced in size so that the edge was palpable at the costal margin. Solution of potassium arsenite was continued, but within a few months the leukocyte count and the percentage of immature cells again began to rise and nucleated red blood cells appeared in the peripheral blood. The spleen gradually increased in size and the patient developed fatigue, non-productive cough and night sweats. In August, roentgen therapy was again begun.

Discussion

It is apparent from the above case reports and charts that solution of potassium arsenite is an effective palliative agent in the treatment of chronic myelogenous leukemia. Symptomatic improvement was reported by the majority of patients soon after the administration of the drug was begun. In several instances, symptoms referable to the leukemia completely (but temporarily) disappeared. As a rule symptomatic improvement was accompanied by gain in weight, reduction in the size of the spleen and by improvement in the blood picture.

The hematologic changes in each patient are presented in detail in the charts. Soon after the toxic dose of arsenic was reached, in the characteristic response, the total leukocyte count began to fall sharply and in many instances approached the normal value. Decrease in the total white blood cell count was accompanied by a diminution in the percentage of immature cells, so that the white blood cell picture as a whole approached normal. The most striking response was observed in M. V.; for a period of several months the only abnormality present in the leukocyte counts was the presence of less than 5 per cent of myelocytes. The degree of hematologic improve-

ment varied from patient to patient, and in the same patient with successive courses of the drug. For example, J. N. experienced two striking hematologic and symptomatic remissions. The third course of Fowler's solution resulted in no significant change in the total or the differential leukocyte counts, but he remained symptom free for a period of 18 months, during which administration of the drug was continued. After a rest period during which roentgen therapy was used, arsenic again resulted in a striking, but temporary, hematologic and clinical remission. A similar variability in response was observed in M. T. and in E. G. with successive courses of the drug.

Anemia, which was present to some degree in all cases, was favorably affected. As a rule, increase in the red blood cell count and hemoglobin did not occur until a significant reduction in the total white blood cell count had taken place. In one patient (D. S.) a reticulocyte response was observed, followed by a sharp increase in the red blood cells and hemoglobin. It should be noted in the chart that the maximum reticulocyte response occurred before the administration of iron. It is possible that improvement in the anemia was dependent on the changes in the white blood cell picture, rather than constituting a direct effect of the arsenic. When nucleated red blood cells were present in the smears before the administration of Fowler's solution, they disappeared from the peripheral blood as the white blood cell picture and the anemia improved. Although there was originally no significant decrease in platelets in any of the patients studied, a favorable response to the arsenic therapy was usually accompanied by an increase in the platelets, easily detected in the smears.

Omission of the drug resulted, in a few weeks, in return of symptoms, increase in the size of the spleen and increase in both the total leukocyte count and the percentage of immature cells.

In attempting to maintain the dose of solution of potassium arsenite as near as possible to the minimum toxic level, each patient experienced repeated toxic symptoms. These included diarrhea, anorexia, nausea and vomiting, itching and puffiness of the eyelids, lacrimation and generalized itching of the skin. Three patients developed localized skin eruptions, characterized by small areas of erythema, dryness, scaling and itching. Three patients complained of tingling in the fingers and toes. In one individual, the soles of the feet became diffusely reddened, tender and slightly swollen. In one instance, herpes zoster of the ophthalmic division of the fifth nerve appeared while Fowler's solution was being administered. It is of interest that herpes zoster appeared in one of Forkner's patients under similar circumstances. Symptoms of arsenic toxicity disappeared within a few days after reduction in dose or omission of the drug. No alarming or serious reactions were encountered. Evidence of hepatic, renal or serious skin lesions was not observed. One patient (M. V.) developed a generalized pigmentation of the skin after taking large amounts of the drug for several months;

the continued administration of arsenic resulted only in very gradual intensification of the pigmentation.

Serious bone marrow depression has occasionally occurred due to the arsphenamines but has been described only after the use of those arsenic preparations which contain the benzine ring. Aplastic anemia, agranulocytosis, and thrombocytopenic purpura are not mentioned either in the literature or in the pharmacologic texts, even as rare manifestations of inorganic arsenic poisoning. Hydrogen arsenide causes a severe anemia in both man and the experimental animal, but here the anemia is due to the markedly hemolytic action of this particular compound.[3] Although there is apparently no danger of inducing bone marrow aplasia, the danger of other serious manifestations of arsenic poisoning must be continually kept in mind in giving, over long periods of time, the large doses of Fowler's solution necessary to induce symptomatic and hematologic remissions in leukemia. Unless frequent and careful clinical observations can be made, this form of therapy should not be used. The prolonged use of such a potentially dangerous drug, under the above conditions, is considered justified in view of the uniformly serious prognosis of the disease.

The mechanism of the action of solution of potassium arsenite in chronic myelogenous leukemia is not clear. Wichels and Hofer [4] observed a reticulocyte response in normal individuals after the administration of toxic doses of the drug. Isaacs,[5] working with white mice, concluded that arsenic solutions had a depressing effect on the bone marrow resulting in a decrease in the production of red blood cells. The effect of inorganic arsenic on the granulopoietic apparatus apparently has not been studied. The beneficial results observed in leukemia are apparently due in large measure to an inhibitory effect on the abnormal process of granulopoietic activity, resulting temporarily in a tendency for the involved structures to return to normal. This view is strengthened by the observation by Forkner and Scott [1] of return to red marrow in one patient in whom bone marrow biopsy was done after arsenic therapy. This inhibitory effect is apparently incomplete and temporary; symptomatic and hematologic relapse occurs after prolonged administration of the drug in adequate dosage. Further study of the effect of inorganic arsenic preparations on the blood and bone marrow of the human and of the experimental animal is needed.

Although roentgen therapy has been used in the treatment of several of the patients reported, conclusions as to the relative merits of roentgen and arsenic therapy are not justified. The number of cases is small, and in many instances less than the optimum amount of roentgen-ray therapy was given. However, the response in individual patients treated with Fowler's solution compares favorably with the reported symptomatic and hematologic response of patients adequately treated with roentgen therapy.[6] This similarity in response of the patient with chronic myeloid leukemia to arsenic and to irradiation has been previously noted.[1] In considering the relative

merits of the two therapeutic procedures, several points should be borne in mind. Solution of potassium arsenite is relatively cheap, is readily available and does not require complicated and expensive equipment, or special technical experience on the part of the attending physician. Frequent clinical and hematological observations are essential, regardless of the method of therapy employed. While by no means all patients who receive roentgen-ray therapy have reactions, patients who have experienced both much prefer the repeated but usually mild symptoms of arsenic toxicity to the more severe and frequently incapacitating reactions which sometimes follow roentgen therapy. The alarming and frequently fatal bone marrow depression which may follow the irradiation therapy of chronic leukemia has not been reported in the small number of patients treated with Fowler's solution. A more extensive experience with the drug may reveal equally serious manifestations in unfavorable cases. It is apparent that arsenic is merely a palliative measure, with temporary effect, as is the case with roentgen therapy. However, an apparently effective agent is available for trial in those patients who become refractory to the effect of roentgen-rays. It is probable that arsenic may be most advantageously used in conjunction with or alternating with irradiation. Apparently the development of refractoriness to one or the other does not preclude the effective use of the alternative agent or a subsequent response to the original therapeutic measure. The question as to whether arsenic, used alone or in conjunction with irradiation, will appreciably prolong the life of the patient with chronic myeloid leukemia cannot be answered at the present time.

Summary

1. Seven patients with chronic myelogenous leukemia, who have received one or more prolonged courses of solution of potassium arsenite, are described.

2. Solution of potassium arsenite is apparently an effective palliative agent in the treatment of chronic myelogenous leukemia.

3. In our experience, the drug is most effective if given in rapidly increasing doses until toxic symptoms appear and then continued in amounts as large as tolerated. Such a régime has been maintained for periods in excess of one year without serious reactions.

4. Solution of potassium arsenite administered in toxic or subtoxic doses to patients with chronic myelogenous leukemia usually results in (*a*) symptomatic improvement, (*b*) reduction in the size of the spleen, (*c*) decrease in the total white blood cell count, (*d*) decrease in the number of immature cells and in the number of nucleated red blood cells in the peripheral blood, (*e*) improvement in the anemia, (*f*) increase in platelets. Such evidences of improvement vary in degree and duration. Symptomatic and hematologic relapse may occur during the continued administration of the drug.

5. It appears that solution of potassium arsenite may be most advantageously used in the treatment of chronic myelogenous leukemia in conjunction with, or alternating with, courses of roentgen therapy.

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ADOLESCENT DISTURBANCES OF ENDOCRINE FUNCTION; THE IMPORTANCE OF THEIR RECOGNITION AND TREATMENT *

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It is manifestly impossible to discuss in a single article all the disturbances of endocrine function that may be encountered during the period of adolescence. I have, therefore, selected one type of dysfunction which is peculiarly related to that period, hypofunction of the anterior lobe of the pituitary gland.

It has long been known that the pituitary was a factor in the abnormalities of skeletal growth which are responsible for gigantism and dwarfism, but its responsibility for disturbances of maturation has been established more recently, and is still imperfectly understood. We have surmised that aberrations of that process were caused by functional disturbances of one or another of the endocrine glands, but have been unable until recently to identify the specific factors responsible for them. This fact, coupled with the observation that not a few of these disturbances of growth and development apparently corrected themselves completely by the time the age of maturity was reached, has resulted in our adopting an attitude of optimistic expectancy in regard to them. The ability of the individual to "outgrow" an adolescent arrest of development has been observed so frequently that it has been depended upon to meet the situation until its failure to do so was demonstrated after the growth impulse ceased. If the failure affects bodily growth markedly, its result is obvious, but if, as more commonly occurs, it results only, or chiefly, in incomplete maturity of the reproductive system, the condition often escapes notice, until symptoms referable to the genital organs direct attention to their incomplete development—too late, as a rule, to correct the defect.

Although no statistics are available concerning the frequency with which significant hypofunctional pituitary disturbances occur during adolescence, evidence is accumulating that they do so more often than has been realized, and that they are successfully "outgrown," or spontaneously normalized, less frequently than we have supposed, so that at present the physician finds himself in a dilemma when confronted by an adolescent patient with definite evidence of genital hypoplasia. Will the underlying pituitary hypofunction correct itself early enough and completely enough to achieve normal adult genital development, or does it require help, and if so, is effective help available?

In an effort to find the answer to these questions I have analyzed the records of two groups of patients. The first is composed of 97 couples

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TABLE I

Genital Development and Endocrine Function

(97 Females)

	Endocrinopathy Present								*Adolescent Endocrinopathy Present function normal								Total Endocrinopathies
Genital Development	T−	T+	P−	P+	G−	G+	A−	A+	T−	T+	P−	P+	G−	G+	A−	A+	
Normal (49 patients)	2	1	5	0	4	0	0	0	0	0	2	0	0	0	0	0	14 (28.5%)
Hypoplastic (44 patients)	1	0	22	0	11	0	0	0	0	0	10	0	0	0	0	0	44 (100%)
Undetermined (3 patients) †	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	2 (66.6%)
Atrophic (1 patient)	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (100%)

* Diagnosis from history and bodily configuration.

† Measurements impossible because of pelvic tumors.

The several foci involved are indicated by T for thyroid, P for pituitary, G for gonad, and A for adrenal. The minus sign (−) indicates a depression of function; the plus sign (+) a hyperactivity.

whose marriages were sterile, and in whom a complete study of the causes of sterility was made.[1] From such a study some idea of the incidence of genital hypoplasia and the disturbances associated with it is obtained. The second group is composed of patients who have been treated for hypofunction of the anterior pituitary lobe and the resulting genital hypoplasia, and offers evidence from which a working hypothesis concerning the value of treatment can be constructed.

Table 1 shows the incidence of normal and hypoplastic genital development in the women of this series, and the association of existing or preexisting endocrinopathies in the two subgroups. The diagnosis of pelvic hypoplasia was made by vaginal examination and the determination of the uterine index by an independent observer.[1] Among the patients with normal genital development there were 12 who showed clinical and laboratory evidence of co-existing endocrine disturbance, as contrasted with 34 women with genital hypoplasia who showed, by the same criteria, evidence of active endocrine disturbances. In both groups, the anterior pituitary was the gland most frequently at fault, with ovarian hypofunction of the primary type, next. Adolescent endocrine disturbances, which had spontaneously corrected themselves, were found in two patients with normal genital development, and in 10 with genital hypoplasia.

A similar analysis of the males, using spermatogenesis as the criterion of normal gonadal development, is shown in table 2. Again the preponder-

TABLE II

Spermatogenesis and Endocrine Function in 97 Adult Males *

Spermatogenesis	T−	T+	P−	P+	G−	G+	A−	A+	Total Endocrine
Normal 34 pts.	4	0	0	0	0	0	0	0	4 (11.7%)
Defective 63 pts.	13	0	25	0	12†	0	0	0	50 (79.3%)

* The examinations of these patients were made by Dr. S. N. Vose.

† Six patients showed testicular hypoplasia. Six showed cryptorchidism. These conditions are probably the result of adolescent pituitary hypofunction, now compensated.

ance of endocrinopathies, and in particular anterior pituitary hypofunction, in the group with defective spermatogenesis is striking, in contrast to their relatively low incidence in the group with normal gonadal function. None of the normal group shows convincing evidence suggesting adolescent endocrine disturbance, while unmistakable stigmata of that condition, without metabolic disturbance at the time of examination, were found in 12 of the patients in the defective group. The figures show a surprisingly high incidence of defective spermatogenesis among the males. In part this may be due to an exacting standard of normality which included not only the number of spermatozoa, but their morphology, duration of motility, and percentage of abnormal forms as criteria. However, the figures of Bland and

his associates,[2] which show more than 50 per cent of deficient spermatogenesis in the males of his series, agree essentially with ours in indicating that whatever the actual percentage may be, there is a very high incidence of defective spermatogenesis in males whose marriages are sterile. Such subnormal function, according to the work of Evans and his associates,[3] is produced when the normal gonad stimulating hormone of the anterior pituitary is lacking, and its high incidence in these patients indicates a correspondingly frequent occurrence of hypofunctional pituitary disturbances, beginning probably during adolescence. The considerable number of patients with thyroid hypofunction serves as a warning, however, that pituitary hypofunction cannot be taken for granted whenever defective spermatogenesis is discovered.

Table 3 shows the incidence of normal and abnormal menstruation in the women composing our series. The correlation between normal genital development and normal menstruation, on the one hand, and genital hypoplasia and oligomenorrhea on the other, indicates that a definite relation between normal development and normal menstrual function exists, and that extremely short, scant, or infrequent menstrual periods are an indication of either genital hypoplasia or, in its absence, of ovarian pathology.

TABLE III

Genital Development and Menstrual Function in 97 Females. (Sterile Marriages)

Genital Development	Menstruation Normal	Polymenorrhea	Oligomenorrhea	Dysmenorrhea
Normal (49 patients)	29 patients	1 patient	18 patients (7 = cystic ovaries) (1 = premenopausal)	1 patient
Hypoplastic (44 patients)	4 patients	4 patients	32 patients (2 = cystic ovaries)	*13 patients
Atrophic (1 patient)	0 patients	0 patients	1 patient	0 patients
Condition undetermined (organic pathology) (3 patients)	3 patients	0 patients	0 patients	0 patients

* Nine patients had both oligomenorrhea and dysmenorrhea.

There is at present some disagreement concerning what is normal menstruation. Boynton,[4] King,[5] and Allen [6] have investigated the menstrual rhythm in healthy women, and have reached the conclusion that irregular menstruation is not uncommon among them, and Anspach and Hoffman [7] have questioned the truth of the idea that most healthy women menstruate regularly and at 28 day intervals. Much of the significance of their findings depends upon what they mean by the word "health." It is obvious that perfect health, as the term is usually understood, can and does exist without complete development of the genital organs, and without their normal function. In our own series, none of the patients complained of ill health, nor

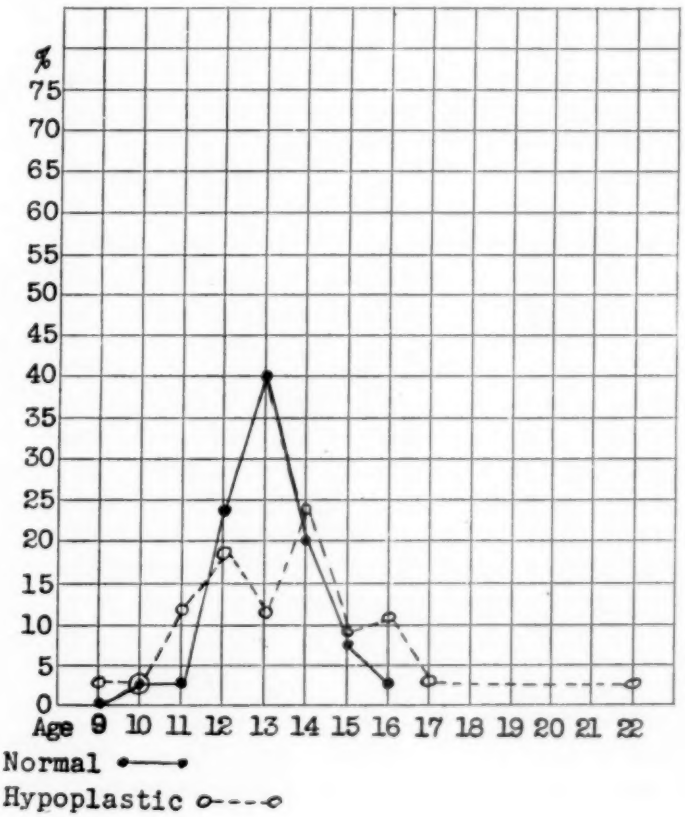
was organic disease, other than focal infection or moderate anemia, demonstrated in them, yet in those whose periods were abnormal by conventional standards, genital hypoplasia or polycystic ovaries existed in a significant majority. It is quite possible that undetected hypoplasia was the cause of the " abnormal " menstrual periods in the women investigated by the writers just cited.

In contrast to the differences of opinion concerning so-called normal menstruation, there is fairly general agreement concerning the normal age of menarche. Englemann [8] in a study of 10,000 patients, found that the average age of menarche in American born women living in this country was 13.9 years. Meaker's [1] figures, from over 2,000 patients, show that menarche occurred in 80 per cent before the fifteenth birthday, so that it seems justifiable to regard the event as delayed when it takes place after that age has been reached.

An analysis of our own series (table 4) shows that there was a definite lag in the age of menarche in those patients who had reached adult life with-

TABLE IV

Age of Menarche in Patients with Normal and Hypoplastic Genital Development



out achieving complete sexual maturity. It likewise suggests that early menarche, before the eleventh year, does not insure normal developmental progress throughout adolescence.

The percentage figures for the "normal" group agree essentially with those given by Englemann [8] and Meaker,[1] while those of the "hypoplastic group" show retardation of the onset of menstruation. From the point of view of diagnosis and treatment, it seems justifiable to conclude that if regular menstrual rhythm has not been established by the middle of the fourteenth year, an investigation of the patient's organic and metabolic condition is justified, and that if it is still absent at the beginning of her fifteenth year, appropriate treatment of the associated defect, again determined by careful and complete study, should be instituted if it is available.

In contrast to the female, the male exhibits no sharply defined events characteristic of adolescence which can be accurately timed. There is, however, some less dramatic evidence to indicate that similar retardation of development occurs in males. The most definite is delay or failure of testicular descent which, if it persists beyond the normal age of puberty, is generally believed to result in permanent depression or even total failure of spermatogenetic function. It is impossible to determine the incidence of cryptorchidism in civil life, but the records of the United States Army Medical Department [9] showed that among the troops in the late war it occurred in three per thousand individuals. In our series of men whose marriages were sterile, it was found 12 times among 97 patients, associated with defective spermatogenesis in every instance.

From the evidence assembled in the foregoing analysis, it seems justifiable to draw certain conclusions, which if not completely proved, afford at least a fair working hypothesis for further investigation. These conclusions are: First, that in both males and females, hypoplastic genital development is more common than has been supposed. Second, that such hypoplastic development is generally the result of a hypofunctional disturbance of the anterior pituitary gland, which in all probability begins during adolescence, and in the majority of individuals persists, if untreated, into adult years. Third, whether the pituitary hypofunction does so persist, or as may occur in a minority of cases, normalizes spontaneously, the defect of genital development tends to be permanent throughout the reproductive period. It, therefore, seems clear that treatment, if it is to be effective in preventing these developmental defects, should be applied before the end of the normal period of development.

There is, however, a lack of agreement concerning the value of treatment, arising from the conflicting results of animal experimentation and clinical experience. Only lately has it become clear that many of these conflicts are due to species variations. These variations have been recently emphasized by Loeb and his associates [10] who have shown that the effects observed in any experiment depend not only on the species of the test animal, but also

upon the species from which the extract employed was derived. It must be clear, therefore, that many of the apparently conflicting reports in the literature are not truly conflicting, since the experiments upon which they are based are not identical. It must also be equally clear that the effect of a given endocrine extract upon human beings cannot be accurately predicted from results observed in any other species. Such observations furnish the clinician with a general conception of the response to be expected, but its exact nature can be determined only by the study of patients before, during, and for a sufficient time after treatment to determine its permanent effect. Such studies are difficult to carry out in adolescent patients for obvious reasons. One cannot do vaginal examinations and endometrial biopsies, nor determine the uterine index, in adolescent girls, nor can one study the spermatogenetic function in adolescent boys. However, by using all the methods that can be fairly applied to each patient, it is possible gradually to accumulate a series in which the condition before treatment, and the response to it, can be established with reasonable certainty.

Table 5 shows the results of treatment in two groups of women so studied who exhibited, before treatment, definite evidence of anterior pituitary hypofunction and associated genital hypoplasia. The latter condition was determined by rectal pelvic examination in the adolescent patients, by

TABLE V

Results of Treatment

End Result	29 Adolescents		21 Adults	
	Amenorrhea	Menorrhagia	Amenorrhea	Menorrhagia
Well	71+%	62+%	30%	27+%
Mod. improvement	14+%	0	10%	18+%
Slow improvement	0	0	10%	36+%
No improvement	14+%	37+%	50%	18+%

vaginal examination in the adults. The diagnosis of pituitary hypofunction was based upon history, physical examination, and metabolic studies. For convenience in tabulation, the patients have been grouped according to the type of menstrual disturbance which constituted their chief complaint. The term " end result " is used to indicate the condition existing six to 12 months after treatment had been omitted, and applies specifically to the menstrual disturbance and its associated genital hypoplasia. Each patient was treated with the same preparation of the anterior pituitary-like hormone derived from pregnancy urine.* The only variable factor was the duration of treat-

* The specific preparation used was Antuitrin S (Parke, Davis Co.).

ment, which ranged between three and 12 months, according to the promptness of the response obtained.

The number of patients on whom it has been possible to carry out these controlled observations is small, and hard and fast conclusions cannot be drawn from the series. The obvious difference in the results of treatment in the two groups, however, is larger than chance would account for, and suggests that the age factor may be an important one in determining the response. This idea receives support from observations on animals. Hertz and Hisaw [11] have shown that the female chinchilla rabbit four weeks old shows no response to a dosage of pituitary extract ample to elicit a maximal response in a rabbit of the same breed when 12 or 13 weeks old. Smith,[12] commenting on this fact, observes "From conditions found in women it may be surmised that after a certain degree of aging the reproductive organs lose their capacity to respond to the gonad stimulating hormone, for after the menopause, follicle stimulating hormone may be present in large amounts, yet reproductive cycles cease." "It is evident," he continues, "that the response elicited by injections of the pituitary or any other hormone is dependent on at least two factors: namely, the stimulating capacity or potency of the dosage given and the responsive capacity of the receptor tissue or organs." The results presented in table 5 suggest at least that the responsive capacity of the human ovary reaches its maximum during adolescence.

Just when this responsive capacity of the human gonads is initiated is not known, but certain clinical evidence shows that it is present, in some degree, before puberty, at least in the male. This evidence is derived from the treatment of cryptorchidism with pregnancy urine extract, concerning which there are numerous reports in the literature. Rubenstein [13] has reported the results of treatment of a patient ten and a half years old who had dystrophia adiposo-genitalis and intra-abdominal testes. The left testis entered the inguinal canal and could be pushed into the scrotum after six injections, totalling 250 rat units. After five months' treatment it had descended completely, the right one partially, and both had increased in size. In contrast, Brosius [14] reports no effect from similar treatment in a pituitary dwarf 38 years old. Dorff [15] has recently published a careful study of 14 (?) male children with maldevelopment and maldescent of the testes. He calls attention to the fact that response is slow, but that it was most rapid in the patients who were close to puberty. Sexton [16] has reported satisfactory response to treatment in a boy 18 years old with double cryptorchidism. It seems apparent from these results that the treatment of genital hypoplasia is about equally effective in both sexes, and that its effectiveness is influenced to a considerable degree by the age of the patient, reaching its maximum at or about puberty, and showing a decided diminution in adult life.

As a corollary, treatment for that condition should be begun in time to

take advantage of the capacity for response. Doing so may involve the occasional treatment of a patient who would have achieved normal development without help, but failure to do so means the acceptance of an unjustifiable handicap. I wish to emphasize again, however, my statement that treatment should not be instituted until a painstaking and complete study has identified the causative factor or factors responsible for the individual patient's developmental delay.

Conclusion

In conclusion, I wish to restate briefly the working hypothesis which seems to be justified by the evidence presented.

Genital hypoplasia, anatomical or physiological, is more common than is generally appreciated. It is caused, in the majority of individuals, by a functional depression of the activity of the anterior lobe of the hypophysis, developing during the pubertal or adolescent periods, but other possible causes, endocrine and non-endocrine, must be recognized. In the female, its existence is suggested by any significant abnormality of the menarche or menstrual rhythm, and can be proved by appropriate examinations. Its causative factors can also be demonstrated by careful study. In the male, the diagnosis is often more difficult to establish before adult age is reached except when physiological hypoplasia is accompanied by obvious anatomical stigmata.

Treatment, to be most effective, must be instituted during the prepubertal or adolescent period.

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OXYGEN TREATMENT AND THYROID ABLATION IN THE TREATMENT OF HEART DISEASE *

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The primary function of the lungs is to transmit to the arterial blood coursing through them an adequate supply of oxygen from the inhaled atmospheric air. During expiration carbon dioxide and water vapor are eliminated. The delivery to the tissues of the oxygen absorbed by the arterial blood is dependent upon the heart, the peripheral circulation, the amount of functioning hemoglobin, the blood volume and other factors. If the heart action is sufficiently impaired, it is unable to maintain adequate blood flow, and the oxygen is supplied to the tissues at a tension less than that needed for proper functioning of the various organs in the body.

In this clinic, an attempt to treat heart failure was made by increasing the amount of oxygen carried by the arterial blood, through the inhalation of high oxygen atmospheres.[1] An added increment of oxygen was provided for the arterial blood with less ventilatory effort, oxygen reached the tissues (including the heart) at higher tensions, oxygen transport was thus more effective; and in certain patients, circulatory compensation was thereby restored.

A more radical therapeutic measure than the provision of an increased arterial oxygen supply is the reduction of the oxygen requirement of the patient through total ablation of the thyroid gland (Blumgart, et al.[2]). In decreasing the needs of the body for oxygen by 25 to 35 per cent, the work required of the heart is so much less than it was that a slowed blood flow becomes adequate to the metabolic demands of the patient. It has, of course, been recognized that the full pursuits of life's activities may be threatened by such a marked reduction in oxygen consumption, approximately to two-thirds of the normal metabolism. The development of hypothyroid states of varying degree, however, is requisite for a significant decrease in the work of the heart.

In each type of therapeutic approach, an adequate amount and tension of oxygen in the tissues of the organism are striven for.

Since we had employed oxygen treatment as a method of facilitating the recovery of patients with cardiac insufficiency, it seemed reasonable to extend it to the procedure of thyroidectomy in heart disease. Twelve patients with heart disease, in whom thyroid ablation was performed with the aid of oxygen treatment, will be presented in this communication.

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Historical

The rationale for the removal of the thyroid gland which Blumgart and his collaborators have carried out in various types of heart failure was derived by them from investigations concerning the effect of the hypothyroid state on blood velocity.[3] According to their reports, the blood velocity varies with the metabolic demands of the body; it is increased in hyperthyroidism and decreased in myxedema. In patients with congestive heart failure, the blood velocity was found to be considerably retarded, in general in proportion to the degree of failure, although the metabolic needs of the body were not lessened. By lowering the basal metabolic rate, i.e., by thyroidectomy, the work the circulation had to do was conspicuously lessened. Equilibrium between the metabolic rate and the blood velocity thus effected was found to restore compensation.

When thyroid ablation was contemplated in our clinic, we proposed to treat these cardiac patients with oxygen prior to operation for a period sufficient to remove as far as possible the signs of cardiac insufficiency, and to employ oxygen during the operation itself and for a period following it. The operative mortality in patients subjected to this operation in various clinics warranted in our minds not only a careful selection of cases but every aid that might be found to lessen the chances of death due to the operation. In a recent series reported by Blumgart et al.,[4] of 50 cases of congestive heart failure, six patients died as a result of the operation. In 25 cases of angina pectoris, none died. In some of their severe cases, our suggestion of preoperative as well as postoperative oxygen treatment was adopted.[5] Since the use of oxygen as an accessory to the procedure of thyroid ablation has appeared to result in a specially smooth postoperative course, so far without operative mortality, the basis for its employment will be reviewed.

It has long been known that the rate of normal heart is especially responsive to changes in the oxygen tension of the inspired air, slowing when pure oxygen is breathed and becoming regularly elevated when the atmosphere has either a diminished concentration or pressure of oxygen. In addition to an increased rate, dilatation of the heart occurs as a result of oxygen-want in normal men at high altitudes (Campbell[6]). In small animals Campbell reported degenerative changes in the myocardium as a result of prolonged exposure to low oxygen atmospheres.[6] Katz and Long,[7] using mammalian heart preparations, have shown that by reducing the oxygen supply to the heart there was rapid dilatation and failure of function, the contractions becoming progressively feebler and conduction slower. When the lactic acid accumulated, as a result of anoxemia, to 2.5 times the normal level, they found complete exhaustion took place, whereas skeletal muscle could withstand up to 4.5 times the normal level, revealing the greater intolerance of the heart to oxygen debt. In experiments on the effect of diphtheria toxin in circulatory failure, G. T. Evans[8] found that the striking feature was sud-

den death and that this could be prevented by artificial pulmonary ventilation. When artificial pulmonary ventilation was not carried out, the heart was found to be almost completely depleted of glycogen. In other words, as Meakins [9] has said, the sudden deaths appeared to be due to a respiratory failure with progressive anoxemia, producing a conspicuous reduction in cardiac glycogen. Under no conditions of severe physical exercise was it possible to lower cardiac glycogen below the normal levels, whereas marked anoxemia depleted cardiac glycogen within a minute or two. Animals breathing atmospheres containing 7 to 6 per cent oxygen gave up as much as two-thirds of their cardiac glycogen.

The heart, therefore, appears to be especially sensitive to oxygen-want. When it is failing it shows its dependence upon the amount of oxygen furnished to it by improving in its function when high concentrations of oxygen are inhaled. Beddard and Pembrey [10] in 1908 observed that the inhalation of oxygen resulted in a decreased pulmonary ventilation in a patient with cardiac insufficiency, which was confirmed subsequently by Campbell, Hunt and Poulton [11] and by Barach and Richards.[1b, 1g] Means and Newburgh [12] in 1915 found a diminished oxygen saturation of the venous blood in cases of cardiac decompensation. Harrop [13] showed that a diminished arterial oxygen saturation was also frequently present. Barach and Woodwell [14] administered 40 to 60 per cent oxygen to cases of cardiac insufficiency for short periods and observed an increase in the arterial saturation and a corresponding elevation of the venous oxygen saturation. In addition, they noticed a definite slowing of the pulse incident to inhalation of high oxygen atmospheres but did not discover alleviation of cardiac dyspnea, due to the brevity of the periods of oxygen administration and the use of a mask or mouthpiece.

In 1927 Campbell and Poulton [15] reported beneficial effects of continuous residence in an oxygen chamber on subjects with dyspnea, especially when related to chronic bronchitis and emphysema, but including also one case of arteriosclerotic myocardial failure. Barach and Richards [1] (1930 to 1935) have presented investigations which reveal in a more detailed manner the special effects of oxygen treatment in congestive heart failure. Their results may be briefly reviewed as follows: Subjective improvement, relief of dyspnea and cough, begins generally in about three hours after entrance to the oxygen chamber and becomes well-marked on the following day. Between the third and sixth days of residence in a high oxygen environment, a diuresis sets in, in the favorable cases, which progresses until the patient is edema-free. This diuresis has been shown to be specifically dependent upon oxygen inhalation and not upon rest in bed, by withdrawal of oxygen in certain instances with cessation of diuresis and recurrence of edema. Objective changes are an increased oxygen saturation of the arterial blood, decreased pulse rate, lowered pulmonary ventilation, fall in blood lactic acid, gradual increase in vital capacity and a characteristic rise in the arterial CO_2

content. The CO_2 curve of the arterial blood may increase from 50 to 100 per cent of the normal level as a response to inhalation of 50 per cent oxygen, representing a mechanism for the elimination of greater amounts of CO_2 in a decreased volume of breathing, which the provision of increased atmospheric oxygen makes possible. This cardio-respiratory rest which oxygen therapy makes possible may be of significance not only as providing relief of symptoms but also as an important factor in the restoration of compensation. When the lungs move more freely, as pulmonary congestion diminishes, the CO_2 curve falls, even in the presence of a high oxygen environment. Deeper ventilation is then employed by the patient for CO_2 elimination rather than the shallow breathing which oxygen therapy makes possible when passive pulmonary congestion is present.

The relief of dyspnea which oxygen therapy induces is sometimes almost immediate as in certain cases of Cheyne-Stokes breathing, sometimes delayed. In a period of several hours, however, the patient will usually notice some relief. The delay is probably due in part to the time required for readjustment of CO_2 level of the blood. This has been discussed in a previous paper. It is evident that a diminished oxygen saturation of the arterial or venous blood is not felt directly as the sensation of dyspnea through its nervous pathways. The relief obtained by oxygen therapy is produced by lessening the effort requirement by enabling not only a lessened total pulmonary ventilation but a shallower type of breathing. The lungs are less locally harassed; the respiratory musculature is relieved of some of its burdensome labored action. Decreased dyspnea results. Peabody and his co-workers [16] emphasized the rôle of lung stiffening in congestive failure (the theory first put forward by von Basch [17]), also the reduction of vital capacity and the mechanical limitations of chest movement. Recently, Harrison [18] has presented elaborate investigations in support of the reflex cause of cardiac dyspnea, minimizing the importance of chemical factors. He states: "As regards the dyspnea produced by mild exertion in patients with congestive heart failure: (1) It cannot be due to inability to increase the cardiac output. . . . (2) It cannot be due to diminished cerebral blood flow. . . . (3) It is evident that the dyspnea of mild exertion is not related to alterations in the oxygen, carbon dioxide, or reaction of the blood, either arterial or venous." He later remarks that attacks of cardiac asthma, when unaccompanied by pulmonary edema, are not likely to be associated with abnormalities in the composition of the arterial blood, and relief of the attack occurs independently of the changes in the composition of the arterial blood.

We would criticize the conclusions of Harrison on two grounds, one of fact and one of logic. As to the first, in the tables presented by Harrison, purporting to show the lack of alteration in blood gases in cardiac asthma, one finds that the majority of patients showed a definite lowering of arterial oxygen saturation, sometimes as low as 86 per cent (see reference 17, pp. 172–173).

On the ground of logic, we believe, as Harrison does, that the primary and immediate cause of the *sensation* of dyspnea, not only in cardiac cases, but in all other instances as well, is to be looked for in the nature of the proprioceptive impulses streaming into the central nervous system from the air passages, lungs and moving framework of the chest. The difficulty with Harrison's point of view, as we see it, is his failure to give due importance to the subject's *breathing requirement,* as distinct from his *breathing capacity.* It is in most instances just as effective, in relieving dyspnea, to reduce the breathing requirement, as it is to increase the breathing capacity. Reduction in breathing requirement, as abundantly shown by Campbell and Poulton, by Richards and Barach, and others, is just what is accomplished by oxygen inhalation in cases of congestive heart failure.

(*a*) Total ventilation is less.

(*b*) Breathing is light and shallow, instead of relatively deep and labored.

(*c*) Oxygen saturation of the arterial blood becomes normal or greater than normal.

(*d*) Arterial CO_2 tension increases, but CO_2 combining capacity increases as well, and pH changes little.

In the accompanying chart (chart 1), a patient with cardio-nephritic disease recorded his tidal volume while breathing air, 100 per cent oxygen, air again and 40 per cent oxygen. It can be seen that the relief of paroxysmal dyspnea, or cardiac asthma, took place immediately after the inhalation of oxygen and that the dyspnea recurred immediately when oxygen was withdrawn. In this case, there was no time for the pathology of the lung itself to change; the dyspnea was *chemically* relieved due to an alteration of the state of the blood gases in the patient which changed the type of respiration as well as decreased total ventilatory requirement.

There is an important aspect to this argument since it has been insufficiently recognized that oxygen therapy in heart disease is based on an actual need of the failing heart muscle for oxygen. In the investigations referred to by Richards and Barach,[1] clinical improvement in patients with congestive heart failure took place both in those in whom arterial anoxemia was present and to a degree in those in whom it was very slightly present or absent. Even without arterial anoxemia, many apparently compensated cardiac patients are in chronic oxygen debt (Uhlenbruck,[19] Knipping [20]), the measurement of which has been used as a criterion for oxygen therapy. There is therefore reason to believe that cardiac patients may make sufficiently severe efforts to cause distress in breathing in order to maintain their blood gases in a normal range, to fulfill oxygen requirement and be released from oxygen debt. Thus, one cannot conclude because the arterial oxygen saturation is normal or only slightly lowered that the threat of anoxemia is not burdensome to the patient.

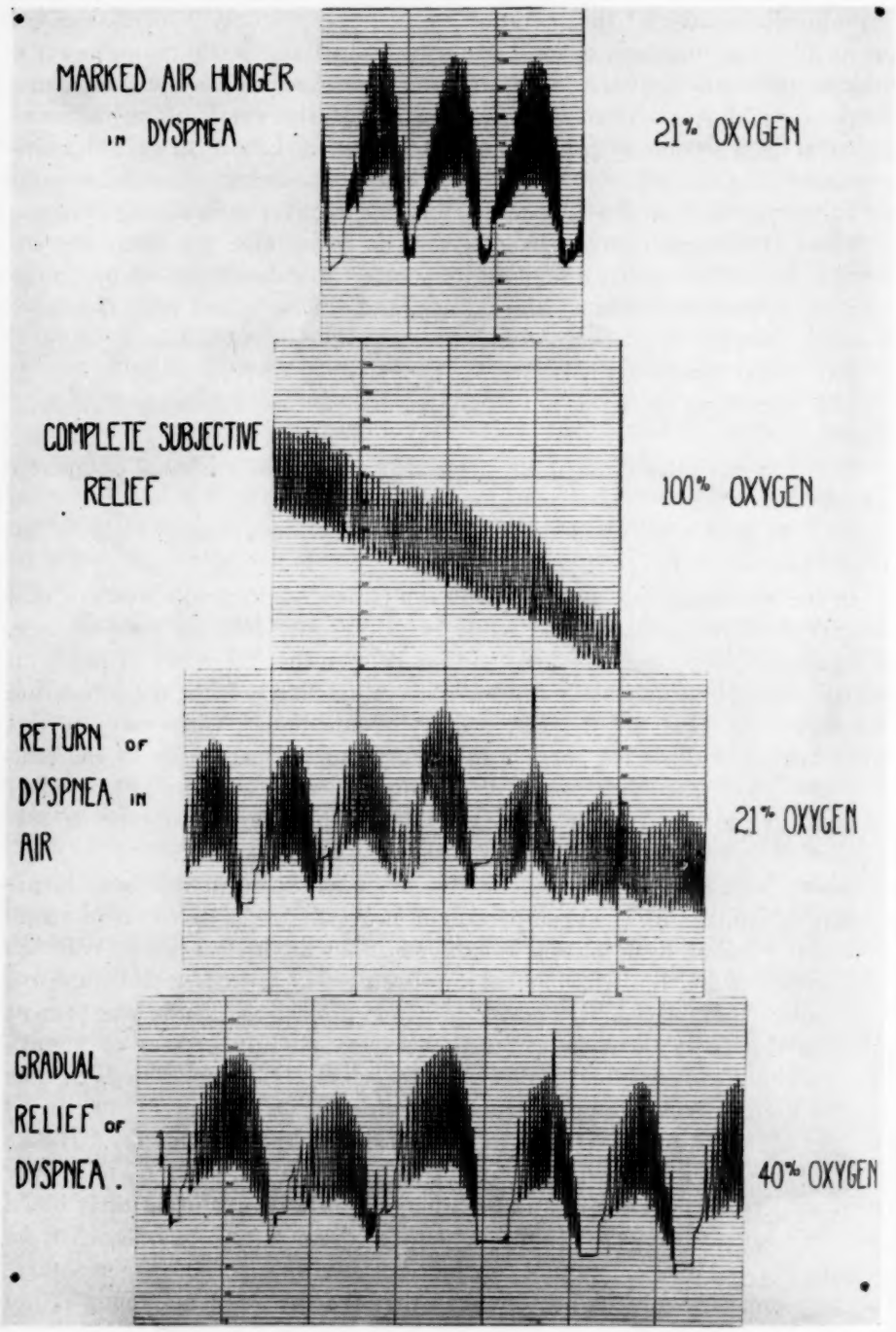


CHART 1. Effect of Oxygen on Cheyne-Stokes Breathing.

The effect of increased atmospheric oxygen is three-fold: (1) The arterial blood contains an increase in the oxygen in physical solution and in that combined with hemoglobin, both of which afford a greater tension of oxygen and a greater delivery of oxygen per unit of blood flow. In other words, a diminished blood flow is made more efficient. In a converse way a small blood flow is made more efficient by a reduction of the oxygen consumption.[2] The second effect of increased atmospheric oxygen is an extension of the first, namely, that an increased delivery of oxygen per unit of blood flow supplies the heart muscle with increased oxygen, upon which it is peculiarly dependent, as noted above. A better contraction of the heart muscle in turn inaugurates a more efficient blood flow, and a virtuous cycle of increased oxygen supply replaces a vicious cycle of oxygen deficit, in which decreasing arterial oxygen tension makes for lessened ability of the heart to contract which in turn lessens blood flow, with an augmentation of the secondary results of cardiac failure, dyspnea and edema.[3] In the third place, as indicated above, increased atmospheric oxygen enables pulmonary ventilation to proceed more efficiently and with actually less effort.

Methods

When a patient was selected for thyroid ablation, he was transferred to the oxygen chamber, oxygen concentration 50 per cent. The chamber was of the thermal circulation type described by one of us.[21] In cases of congestive failure, treatment was continued for two to three weeks or until evidence of decompensation receded. In patients with angina pectoris without congestive failure, a period of four to seven days of oxygen treatment generally preceded operation. The patient on the morning of operation was given a small dose of nembutal, 0.1 to 0.2 gm. A nasal catheter was inserted into the nasopharynx in the chamber and a flow of 5 liters of oxygen per minute begun before the door of the chamber was opened. He was then taken up the elevator and wheeled to the operating room without discontinuance of oxygen, the 220 cu. ft. tank being wheeled behind the patient. Oxygen was continued throughout the operation, which was done under local anesthesia, and the patient returned in a similar manner to the oxygen room. When the concentration was brought up to 50 per cent, the nasal catheter was withdrawn. Generally, a period of four days in the chamber followed, when the oxygen concentration was lowered to 40 per cent for 12 to 24 hours, then to 35 per cent for 12 to 24 hours, when he was removed to a ward or room. If lowering the oxygen concentration provoked too great a rise in pulse rate, i.e., over 10 beats per minute, the oxygen concentration in the chamber was elevated for two or three days and then again gradually lowered. If the patient had been withdrawn from the chamber, a nasal catheter was used for several days if the pulse became unduly increased.

The gas analysis was done by the method of Van Slyke and Neill. The blood volume was determined by the dye method, using brilliant vital red

(of Peters and Van Slyke). The venous pressure was measured by the direct method of Moritz and Tabora.

Results

Of 12 patients upon whom thyroid ablation was performed, five had rheumatic disease with congestive failure; two had arteriosclerotic disease with congestive failure; two had congestive failure with associated coronary sclerosis and anginal pain, and three had coronary arteriosclerosis with anginal pain without congestive failure. All the patients except one had a normal basal metabolism and experienced a complete ablation of the thyroid. One patient had hyperthyroidism with arteriosclerotic heart disease and congestive failure and was treated with oxygen and a partial thyroidectomy. In summary, nine of 12 cases had congestive heart failure prior to treatment.

Case Reports

Case 1. N. G., female, aged 34.

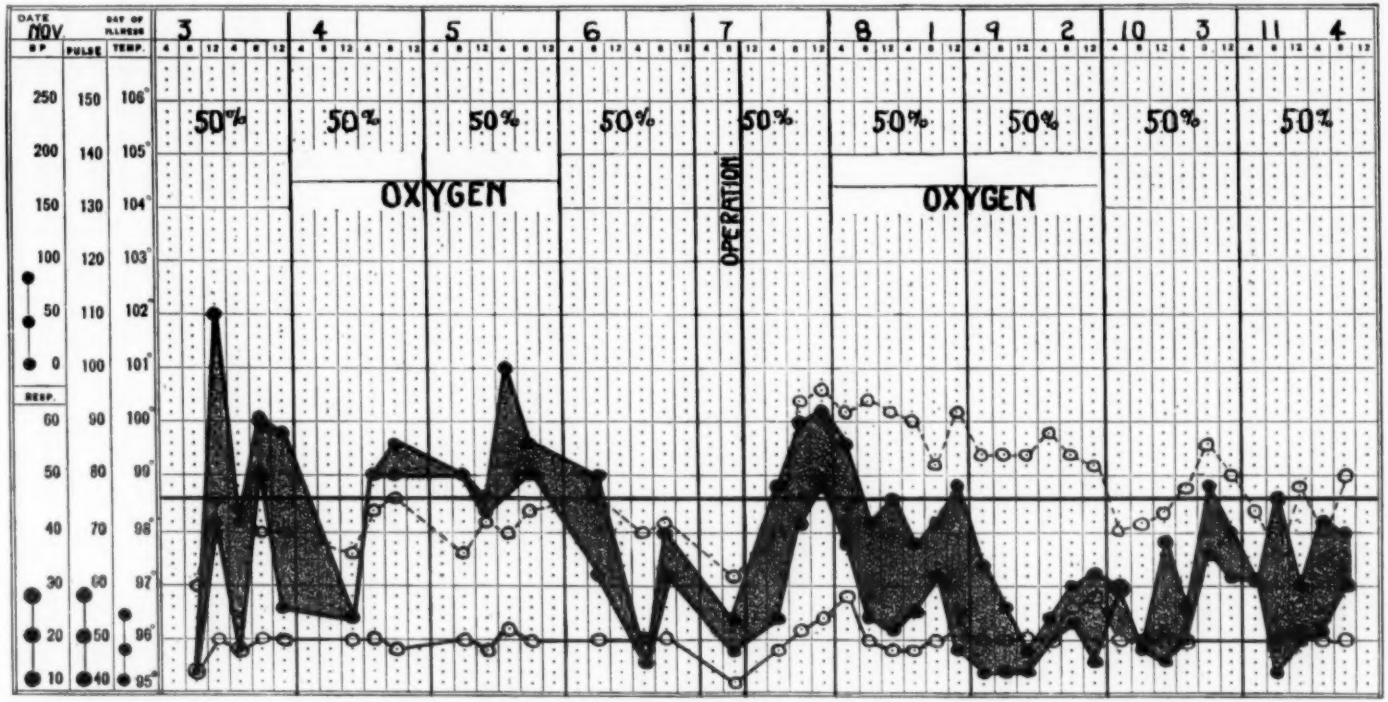
Family History: One daughter had rheumatic fever. *Personal History:* No rheumatic fever but occasional sore throats as a child. Malaria at 14. *P. I.:* Heart lesion first noted 17 years ago during first pregnancy. Six years ago, patient noticed dyspnea on climbing stairs, and for past five years has been practically incapacitated. During the last 18 months she has been confined to bed, with palpitation on the slightest exertion, intermittent edema and recurring ascites which finally necessitated paracentesis at three-week intervals.

Physical Examination: A poorly developed, emaciated, cyanotic, adult woman, not dyspneic at rest. Neck veins dilated. Pupils react to light. Lungs contain râles at both bases. Heart enlarged in all diameters; systolic and diastolic murmurs at apex; blowing diastolic at the base; pulse totally irregular, exceptionally small volume. Blood pressure 80/40 mm. of Hg. Abdomen distended with fluid. Liver hard, felt 7 cm. below costal margin. Slight sacral edema without ankle edema.

Laboratory Findings: Hgb. 84 per cent; r.b.c. 3.8 millions; w.b.c. 4,600; polynuclears 83 per cent. Urine: albumin, heavy trace. Serum protein 7.8 per cent. Electrocardiogram: auricular fibrillation; R_2 and R_3 notched; T_1 diphasic; T_2 and T_3 inverted.

Course. A paracentesis was done the day after admission with considerable relief. She was put in the oxygen chamber (concentration of oxygen 50 per cent), for two weeks when thyroid ablation was performed. A nasal catheter was inserted while the patient was in the chamber and 5 liters of oxygen administered during the transport of patient to and from the operating room and during the operation. Local anesthesia was used. The operation was performed without any signs of cardiac embarrassment. She was kept in the oxygen chamber for one week after operation, the oxygen concentration being gradually lowered the last three days, and then removed to the ward. As shown in chart 1, she had a slight increase in temperature with little change in her cardiac and pulse rates after operation. During the next 10 weeks, her basal metabolism gradually dropped from minus 13 to minus 43 per cent. Eight weeks after operation, she developed enough ascites to require tapping; 2,200 c.c. fluid were removed. She was discharged 14 weeks after operation, unmistakably improved, able to walk the length of the hospital floor without palpitation or dyspnea.

Before operation, her venous pressure varied between 130 and 153; after operation, between 135 and 225. Blood velocity before operation, 25–35; after, 38, 41, 48, 52 (table 1 and chart 2).



OPERATION: Total Thyroidectomy
DIAGNOSIS: 1. Inactive Rheumatic Heart Disease
2. Mitral Stenosis and Insufficiency
3. Tricuspid Valve Insufficiency
4. Chronic Passive Congestion of Liver

CHART 2. Clinical chart before and after thyroid ablation with patient in 50 per cent oxygen atmosphere.

TABLE I

Case 1	Before Operation	After Operation	Remarks
Date	10-17-33 to 11-7-33	11-7-33 to 8-1-35	
Arterial oxygen saturation	94%	93%	Patient had been confined to bed for 18 months prior to operation. She was in oxygen chamber 14 days before and 6 days after operation. Arterial oxygen saturation in oxygen chamber 99 per cent. Ascites recurred for 1 year following operation. Since 10-17-34, no paracentesis necessary.
Hemoglobin	84%	72 to 85%	
Basal metabolism	−13	−18 to −43	
R.B.C. millions per cu. mm.	3.8	3.6 to 4.2	
Vital capacity	900 to 1100	1200 to 1750	
Blood velocity (seconds)	25–35	38, 41, 48, 52	
Venous pressure	130–153	135 to 225	
Arterial pressure	100/60	95/50 to 120/70	
Sedimentation rate		45 mm./1 hr.	
Arterial CO_2 vol. per cent	53.6	55.4	
Blood cholesterol		194 to 205	
Wt. kg.	44	45.8	
Pulse	48–120	40 to 64	

Following her operation, December 7, 1933, patient was able to do more without heart consciousness or dyspnea than she had at any time during the previous five years. She required paracentesis at long intervals for one year and since that time has had no re-accumulation of fluid in her abdomen (from December 17, 1934, to the present time, December 7, 1935). She is up and about the house, does a small amount of shopping, walks in her garden, and has had no break in compensation. She has been kept on 0.1 gm. digitalis daily. Her vital capacity before operation was between 900 and 1,100 c.c. Since operation, it has varied between 1,200 and 1,750 c.c. The electrocardiogram has not altered essentially. The blood velocity is slower, the venous pressure not appreciably different. The blood cholesterol reached a high of 205 mg. per 100 c.c.

The patient was an intelligent Armenian, a writer, with marked emotional instability. For a year after operation, she believed that her writing was impaired by her lowered metabolism, this opinion being shared by an editor to whom she was accustomed to submit material. When her basal metabolism was raised to a level of minus 30 per cent she resumed her writing and the editor referred to said she wrote one of her best stories. It may also be said that her interest in her husband was revived as a result of her better physical health. She regards herself as having been strikingly benefited physically but believes she has been somewhat handicapped in her ability to write. She is on a maintenance dose of ¼ gr. thyroid daily.

The follow-up results in this patient have been remarkably good. Bed-ridden for 18 months prior to operation, requiring paracenteses finally every three weeks,

conscious of her heart beat on the slightest movement, she became a woman able to carry on ambulatory activity without discomfort, being up five to eight hours daily. The signs of facial myxedema have been slight and the mental reaction to her operation has largely subsided. However, she has complained of pains in legs and feet for the past eight months. Noticeable crepitus on movement of the left knee-joint has appeared in the past four months.

Case 2. M. M., female, aged 56.

Personal History: No rheumatic or luetic history. *P. I.:* Ten years ago the patient was in the hospital for four months for cardiac insufficiency; she was discharged on digitalis, able to carry on ambulatory activity. Six weeks before the present admission, her abdomen began to swell, she became dyspneic and during the last three weeks before admission was confined to bed.

Physical Examination: A slight, undernourished and palely cyanotic woman. Pitting edema over sacrum but not in legs. Lungs showed evidence of fluid at right base and moist râles over lower two-thirds of both lungs. Heart enlarged to left and right. Loud systolic and diastolic murmurs at apex. Heart fibrillating. Blood pressure 135/90 mm. of Hg. Abdomen distended with fluid, and liver palpated below the umbilicus.

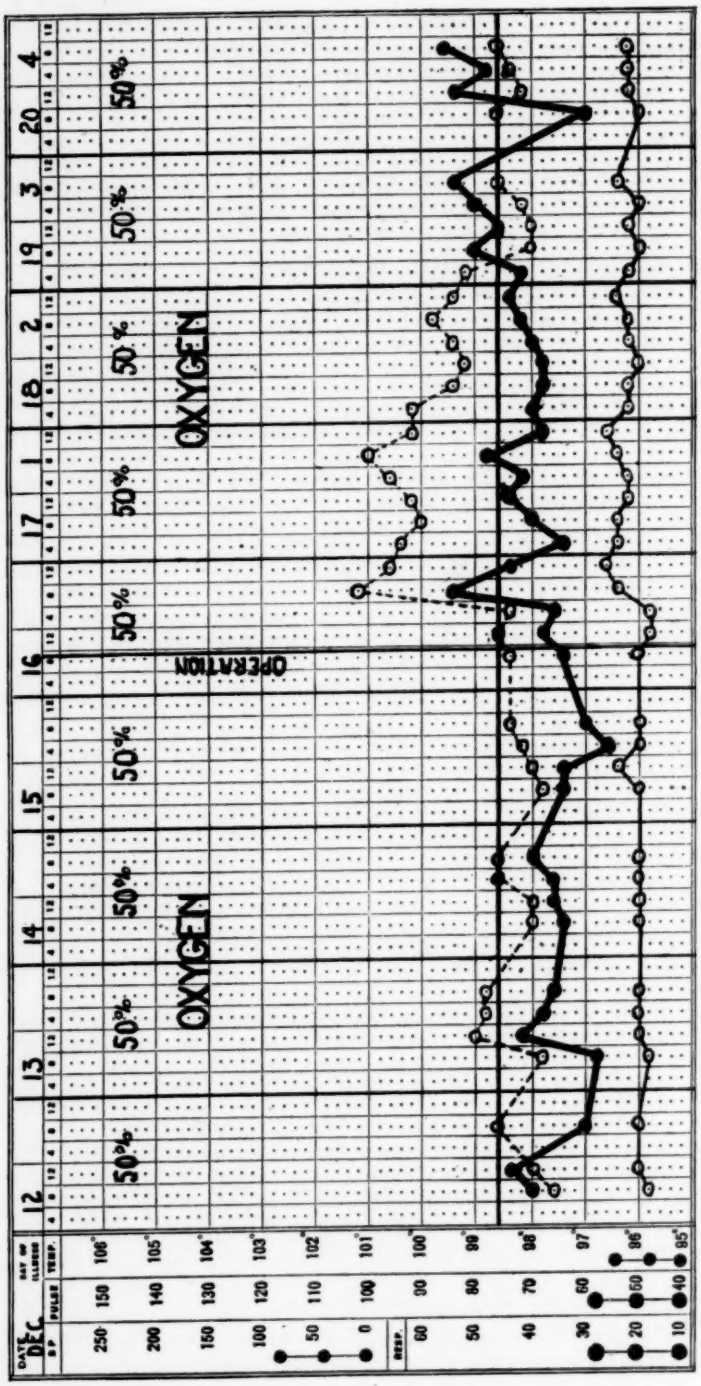
Laboratory Findings: Hgb. 82 per cent; r.b.c. 4.2 millions; w.b.c. 8,000; polynuclears 79 per cent. Serum protein 7.13 per cent. Electrocardiogram: Auricular fibrillation; R_1 notched, T_1 inverted, T_2 and T_3 upright. Blood urea 32 mg. per cent. Course: After five months of routine hospital treatment, the patient was still bed-ridden, unable to regain sufficient compensation to be about in a chair. She was treated for three weeks in the oxygen chamber (oxygen concentration 50 per cent), and became free from dyspnea, orthopnea and heart consciousness. She was operated on while receiving oxygen through a nasal catheter, as outlined. She had scarcely any postoperative reaction (chart 3). She was removed from the chamber seven days after operation.

Basal metabolism dropped from minus 3 per cent before operation to minus 30 per cent one month later, finally falling to minus 42 per cent. Two months after operation the patient was able to walk slowly without dyspnea or heart consciousness. The liver was still palpable 8 cm. below costal margin but there was no evidence of fluid or other sign of cardiac insufficiency. The venous pressure varied before operation from 260 to 53; after, from 175 to 57. The arterial oxygen saturation before operation was 93 per cent; after, 97 per cent. Vital capacity 1,375 before operation; after, 1,050 to 1,675 c.c. Blood cholesterol increased to 264 mg. per 100 c.c. blood. The blood volume was 4,600 before, 4,000 to 4,200 after operation (table 2).

The follow-up results in this patient were very good. She was able to go about, live in an apartment where she had to climb two flights of stairs, and felt comfortable and happy. Despite a basal metabolism that was approximately minus 40 per cent, she had little evidence of facial myxedema except an increased pallor and no distressing symptoms. Small doses of thyroid were given for a short time only, as they resulted in heart consciousness. She was nevertheless mentally alert. She was operated upon December 16, 1933. Except for a brief stay in the hospital in April 1935, for mild symptoms of cardiac insufficiency of five days' duration which quickly responded to rest in bed, she has been quite well. At the present writing (August 1935) she is ambulatory. Without thyroid medication her basal metabolism is minus 37 per cent.

Case 3. A. S., female, aged 22.

Personal History: Patient had rheumatic fever with valvular heart lesion before age of ten. *P. I.:* Four years ago, the patient developed symptoms of acute decompensation in the sixth month of pregnancy. After a rest period, Caesarian sec-



OPERATION: Total Thyroidectomy
DIAGNOSIS: 1. Cardiac Insufficiency
2. Chronic Cardiac Valvular Disease
3. Mitral Stenosis and Insufficiency
4. Auricular Fibrillation
5. Cardiac Hypertrophy
6. Chronic Cardiac Dilatation
7. Posterior Poliomyelitis

CHART 3. Clinical chart before and after thyroid ablation with patient in 50 per cent oxygen atmosphere.

TABLE II

Case 2	Before Operation	After Operation	Remarks
Date	7-3-33 to 12-16-33	12-16-33 to 8-1-35	
Arterial oxygen saturation	93%	97%	Oxygen treatment in chamber, 50 per cent oxygen, was carried out for 3 weeks. Patient lost sensation of dyspnea while in oxygen chamber and was generally improved. Liver was still much enlarged. No fluid in pleural cavities. Data before operation obtained in 3 separate admissions for congestive failure, dyspnea being outstanding symptom. Nasal oxygen, 5 liters per minute, was given during operation. She was in oxygen chamber for 7 days following operation.
Hemoglobin	73 to 86%	74 to 95%	
Basal metabolism	−3%	−20 to −42%	
R.B.C. millions per cu. mm.	4.0 to 5.0	4.0 to 4.8	
Vital capacity	1375	1050 to 1675	
Blood volume	4600	4000 to 4200	
Blood velocity (seconds)	49, 43, 34	41, 52, 25.5	
Venous pressure	260 to 53	175 to 57	
Arterial pressure	104/60 to 150/100	145/70 to 108/65	
Sedimentation rate	20 mm./1 hr.		
Arterial CO_2 vol. per cent	47.0	42.4	
Blood cholesterol mg. per cent		264	
Wt. kg.	42.7 to 48.2	44 to 47	
Pulse	42	60	

tion and sterilization were performed. Since that time she has been admitted to the hospital five times for cardiac insufficiency. Her present attack began two weeks before this admission with edema of ankles, tachycardia, and dyspnea. Eight days ago, coughing and orthopnea appeared.

Physical Examination: A well-developed girl with a hacking cough, without dyspnea or cyanosis. Lungs contain a few râles at the bases. Heart greatly enlarged. Rhythm totally irregular. Systolic thrill and double murmur at apex; diastolic murmur at aortic area. Blood pressure 160/70 mm. of Hg. Liver palpable 7 cm. below costal margin. Edema of feet, ankles and sacrum.

Laboratory Findings: Hgb. 85 per cent; r.b.c. 4.5 millions; w.b.c. 7,600; polynuclears 72 per cent. Electrocardiogram: Auricular fibrillation; T_1 and T_2 upright, T_3 diphasic.

Course: At the end of two months in the hospital, the patient was compensated in bed. She was treated in the oxygen chamber (oxygen concentration 50 per cent) for seven days prior to operation and eight days after under the usual technic. The operation was attended by a minimal reaction. Her basal metabolism, which was plus 6 to minus 10 before operation, was minus 13 per cent on discharge four weeks later, ultimately declining to minus 25 per cent. Vital capacity varied between 1,200 and 1,800 before operation, 1,300 after (table 3).

TABLE III

Case 3	Before Operation	After Operation	Remarks
Date	1-30-34 to 4-3-34	4-3-34 to 12-12-35	
Arterial oxygen saturation	95%	96%	Patient in oxygen chamber, 50 per cent oxygen, 7 days before operation and 8 days after operation. She had 5 admissions for cardiac insufficiency during previous 4 years.
Hemoglobin	74 to 90	65 to 86	
Basal metabolism	+6 to −10	−13 to −25	
R.B.C. millions per cu. mm.	3.8 to 4.8	2.8 to 4.7	
Vital capacity	1200 to 1800	1300	
Blood velocity (seconds)	25	35	
Venous pressure	28	45	
Arterial pressure	105/70 to 160/70	105/65	
Sedimentation rate mm./1 hr.	16 to 57	58	
Arterial CO_2 vol. per cent	55.1	48.5	
Blood cholesterol		217	
Wt. kg.	47 to 49	55	
Pulse	80 to 84	82 to 92	

For three months after operation the patient did well, when palpitation, dyspnea and pain over her heart recurred. Symptoms persisted for seven weeks when she entered the hospital. At this time her hemoglobin was 66 per cent, r.b.c. 2.8 millions with numerous macrocytes. During the nine weeks in the hospital thyroid was first administered and subsequently liver and iron, the hemoglobin rising to 81 per cent and the r.b.c. to 4.0 millions. Six months after discharge, she said she felt "fine" on ambulatory activity. Her basal metabolism was then minus 13 per cent on 1 grain of thyroid daily. She took 0.1 gm. digitalis daily.

Symptoms of cardiac insufficiency recurred seven months later, necessitating readmission to the hospital. However, her basal metabolism had become elevated to plus 5 per cent, which obviously counteracted the effect of thyroidectomy. After four months' hospitalization, during which time thyroid administration was stopped, the basal metabolism dropped to minus 20 per cent and she gradually regained compensation (December 1935).

Although the results in her case were complicated by high thyroid dosage, the amount of work she was capable of performing in her periods of compensation outside the hospital was greater than that she was able to do prior to operation.

Case 4. J. P., male, aged 51 years.

Family History and Personal History: Irrelevant. *P. I.:* Patient began to have recurrent attacks of precordial pain radiating down left arm and dyspnea on exertion five years ago. Three years before the present admission he entered the hospital for alcohol injection. This resulted in a somewhat wider spacing of attacks but was followed by spinal pain and recurrence of anginal attacks. During this

period, he manifested considerable anxiety and depression, so that it was difficult to form a confident appraisal of the etiology of all his complaints.

Physical Examination: An obese, whispering, uncomfortable man sitting in bed, orthopneic and slightly cyanotic. Pupils slightly irregular but reacted to light. Heart greatly enlarged with P.M.I. in sixth space, 15 cm. from mid-sternum. Sounds of poor quality. Blood pressure 150/120 mm. of Hg. Radial artery thickened. Lungs contained moist râles at both bases. Abdomen: Dullness in both flanks but no fluid wave or shifting dullness.

Laboratory Findings: Hgb. 95 per cent; r.b.c. 5.19 millions; w.b.c. 8,600; polynuclears 75 per cent. Urine, few granular casts. Serum protein 7 per cent; nonprotein nitrogen 36.4. Electrocardiogram: sinus rhythm; R_1, R_2 notched; T_1, T_2 inverted; T_3 upright. Indication of incomplete bundle branch block.

Course: After four weeks on the ward, thyroidectomy was performed. He was in the oxygen chamber for eight days prior to operation and five days afterwards. On removal from the chamber, he had a recurrence of chest pain, relieved by nasal catheter which was continued for three days. His pain thereafter seemed to be definitely diminished. However, the patient has done poorly. Operated upon February 8, 1934, he was admitted twice during the following year, with slight congestive failure but mainly because of a depressed hopeless attitude. He has spent all of his time in bed, both in the hospital and at home, complaining of weakness and recurrent chest pain. Basal metabolism one year after operation was minus 28 per cent.

It must be admitted that the operation did not justify itself in his case. His anxiety state with persistent depression made it impossible to evaluate the results of the operation. As seen in the table (table 4), the measurements recorded failed to give any evidence of improvement. The venous pressure and blood volume tended to be higher after thyroidectomy, the arterial oxygen saturation only 1 per cent higher.

TABLE IV

Case 4	Before Operation	After Operation	Remarks
Date	1-16-34 to 2-8-34	2-8-34 to 5-1-35	
Arterial oxygen saturation	92%	93%	Patient was in oxygen chamber 8 days before and 5 days after operation. Recurrence of pain after removal from chamber was treated by nasal catheter for 3 days.
Hemoglobin	103 to 113	85 to 115	
Basal metabolism	−2%	−14 to −27%	
R.B.C. millions per cu. mm.	5.5 to 6.0	4.8 to 5.8	
Vital capacity	2400	2000 to 2700	
Blood volume	4144	5155	
Blood velocity		32 to 52	
Venous pressure	68	83 to 130	
Arterial pressure	152/100	136/92 to 178/128	
Arterial CO_2 vol. per cent	52.0	55.1	
Wt. kg.	73	72 to 74.3	
Pulse	80	74 to 80	

Case 5. W. H., male, aged 51 years.

Family History and Personal History: Irrelevant. *P. I.:* For three years the patient has suffered from recurring, sharp, substernal and epigastric pain, radiating to back and down left arm, increasing steadily in severity and in the frequency of attacks. He had no orthopnea or ankle edema, but his illness prevented him from working for the past year and a half.

Physical Examination: A well-developed pale man of 51. Fundi show slight narrowing of arteries. P.M.I. 11.5 cm. from midsternal line in fifth space. Sinus arrhythmia with numerous extra-systoles. Sounds distant. Soft, blowing systolic murmur at apex; loud rough systolic at aortic area. Radial arteries thickened. Blood pressure 145/90 mm. of Hg. Liver edge felt 4 cm. below costal margin.

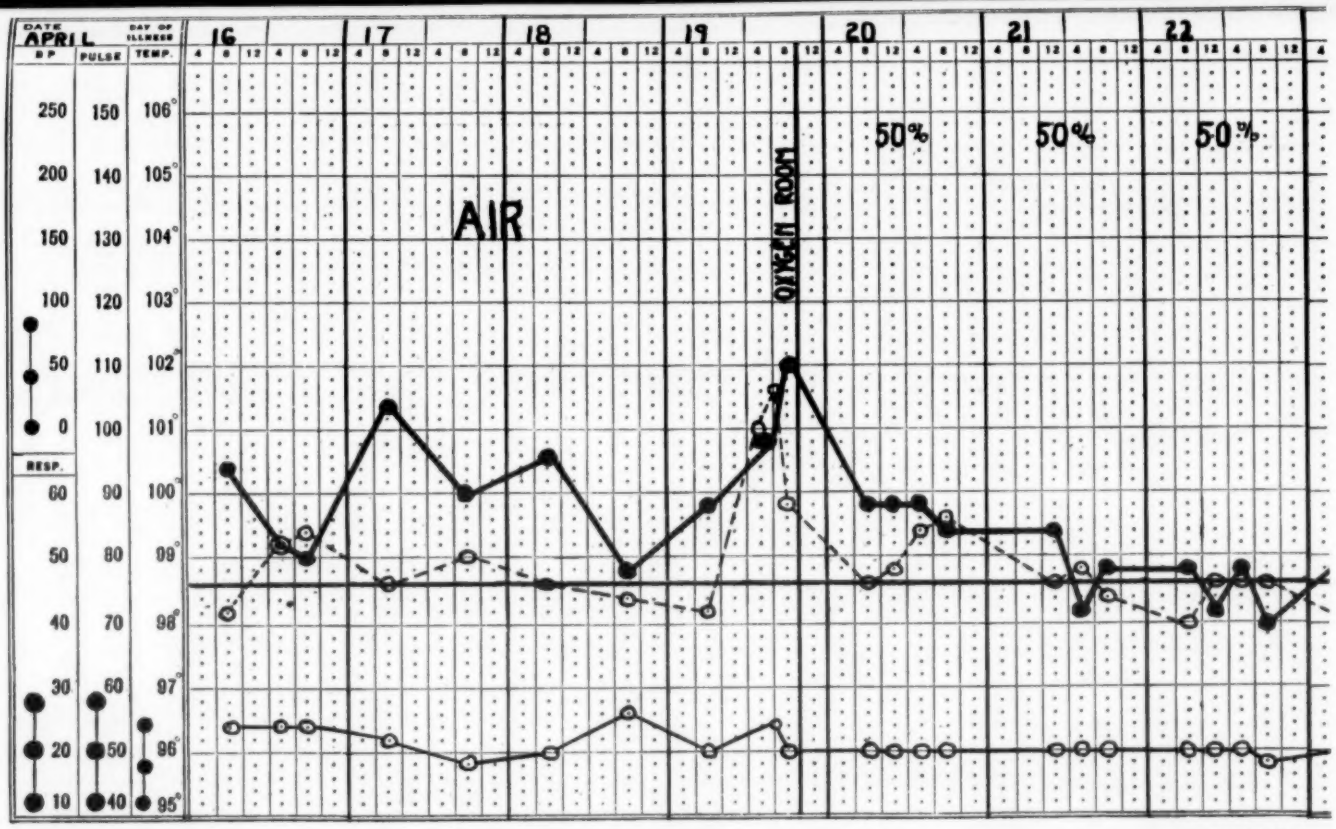
Laboratory Findings: Hgb. 77 per cent; r.b.c. 4.4 millions; w.b.c. 6,100; polynuclears 67 per cent. Blood urea 46 mg. per cent. Electrocardiogram: Ventricular premature beats; R_3 notched, T inverted in all leads.

Course: Patient was treated with 50 per cent oxygen in the oxygen chamber for nine days prior to operation and for 16 days after. The length of the postoperative oxygen treatment was due to the fact that the first attempt at lowering the oxygen concentration, on the fourth to the fifth day after the operation, was followed by rise in the pulse rate and recurrence of substernal pain. The second lowering of the oxygen concentration was uneventful. The operation resulted in a minimal reaction (chart 4 and table 5).

TABLE V

Case 5	Before Operation	After Operation	Remarks
Date	4-14-34 to 4-28-34	4-28-34 to 6-29-34	
Arterial oxygen saturation	96%	97%	Patient was in oxygen chamber 9 days before and 16 days after operation. First attempt at lowering oxygen concentration precipitated rise in pulse rate and recurrence of pain in chest, which was promptly relieved by raising oxygen concentration again to 50 per cent. Second lowering of oxygen concentration was borne without symptoms.
Hemoglobin	77 to 85%	83 to 85%	
Basal metabolism	+24%	−2 to −20%	
R.B.C. millions per cu. mm.	4.5	4.1 to 4.7	
Vital capacity	2950	2500 to 2850	
Blood volume	5700	5000	
Blood velocity	25	25	
Venous pressure	10	25	
Arterial pressure	140/95	138/88 to 152/90	
Arterial CO_2 vol. per cent	48	55.3	
Pulse	108	68 to 100	

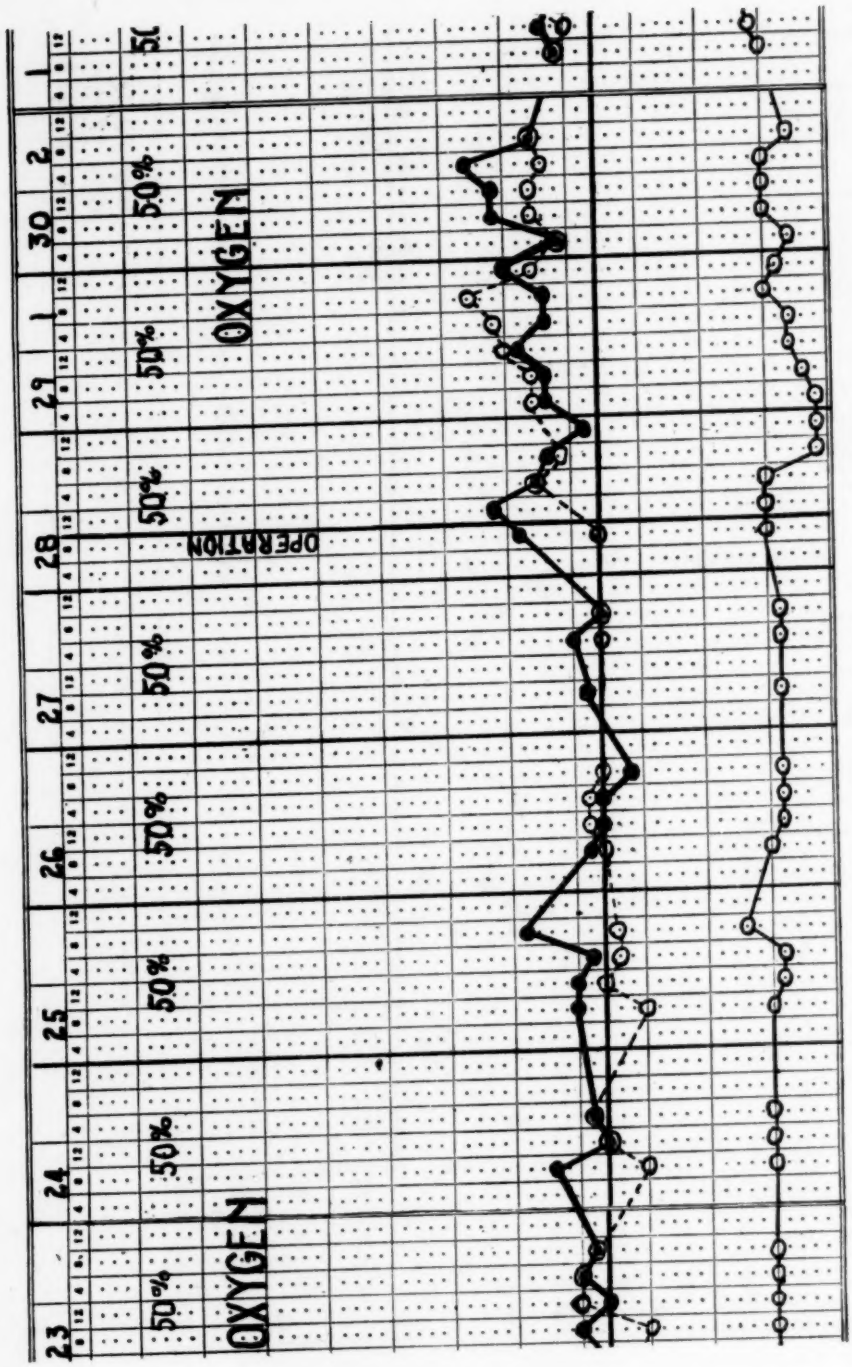
Before operation his basal metabolism was plus 24 per cent; during the five weeks after operation, his lowest basal metabolism was minus 11 per cent. During the last week he began to show improvement, with practically no discomfort on walking the hospital corridor. For one month after leaving the hospital, the patient did well, being able to walk 10 blocks without pain. Symptoms then returned worse than ever, and he reëntered the hospital seven weeks after discharge. On this admission, his



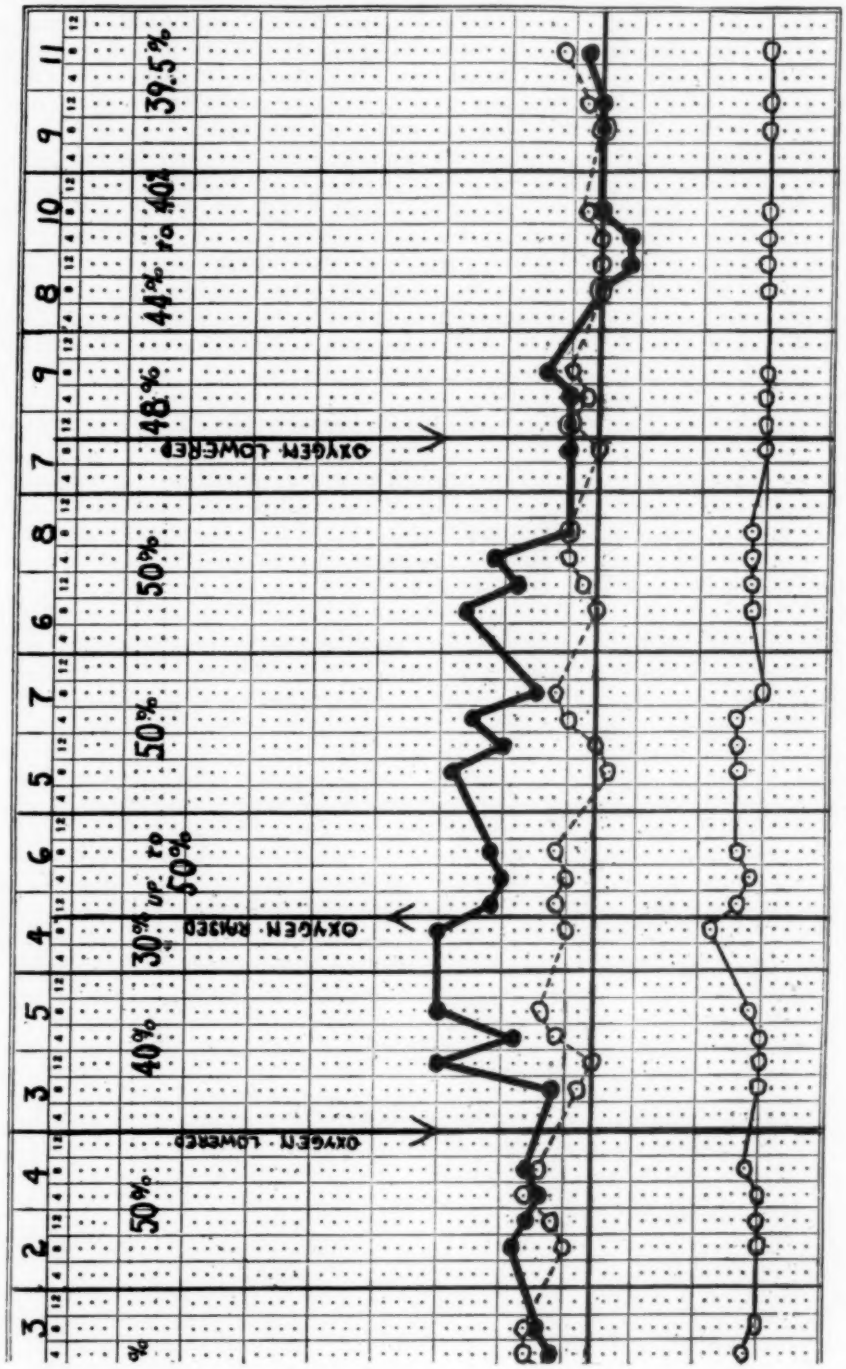
OPERATION: Total Thyroidectomy
DIAGNOSIS: 1. Arteriosclerotic Heart Disease
2. Angina Pectoris
3. Myocardial Fibrosis and Insufficiency

PRE-OPERATIVE PERIOD

CHART 4. Clinical chart showing reduction of pulse rate due to oxygen treatment, minimal postoperative reaction and elevation of pulse on first attempt to lower oxygen concentration.



OPERATIVE PERIOD
CHART 4—*Continued*



POST-OPERATIVE PERIOD
CHART 4—*Continued*

blood count was lower, Hgb. 70 per cent; r.b.c. 3.5 millions. The electrocardiogram showed definite changes; the T waves in Leads I and II were more deeply inverted; T_3 diphasic; R_2 more notched. Blood cholesterol 208 mg. per 100 c.c. The lowest basal metabolism obtained was minus 20 per cent. Radiotherapy to the thyroid gland was begun. Four weeks after admission he began to have severe precordial pain at rest, unrelieved by nitroglycerine. His heart sounds became weak and he was placed in an oxygen tent, oxygen concentration 60 per cent. The next day he felt fairly well when suddenly he had a severe precordial pain and died almost instantly.

It was evident that thyroidectomy did not alter the progressive course of coronary sclerosis in this patient. Such improvement as took place was very temporary. At autopsy, a small nodule of hyperplastic thyroid was found, which accounted for the basal metabolism not reaching lower levels. However, since his preoperative reading was plus 24 per cent, a relative lowering of oxygen consumption did take place. Post-mortem examination revealed marked aortic stenosis with slight generalized coronary sclerosis.

Case 6. S. S., male, aged 57 years.

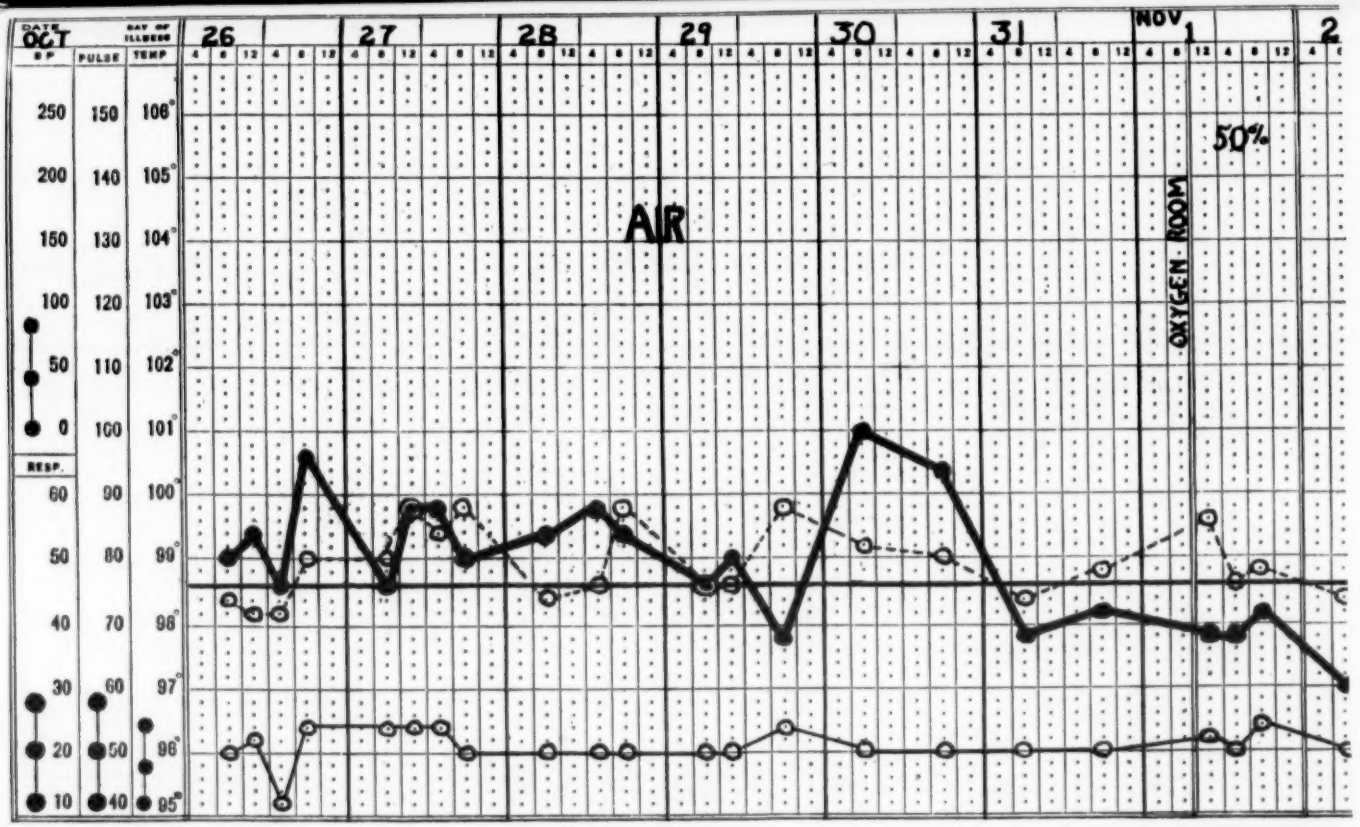
Personal History: Four years ago, the patient developed difficulties in urinating, and was treated two years later by supra-pubic prostatectomy. *P. I.:* Three years ago, he began to be short of breath on exertion. Five months ago, he developed precordial pain on exertion. For four months he has suffered intermittent claudication in the legs. Three and one-half months ago, he went to bed for six weeks because of dyspnea and edema. Precordial oppression has frequently occurred while at rest; walking three blocks brought on pain in chest.

Physical Examination: A plethoric, well-developed man of 57, somewhat orthopneic and dyspneic. Slight arterial tortuosity noted in fundi. Lungs, sibilant râles scattered throughout, with slight dullness at left base. Heart slightly enlarged. Systolic blow at apex. Radial artery sclerotic. No pulsation in dorsalis pedis or posterior tibial arteries. Blood pressure 160/90 mm. of Hg. Varicose veins of legs. Liver edge palpable 3 cm. below costal margin.

Course: He was placed in an oxygen tent (oxygen concentration 50 per cent) and five hours later precordial oppression subsided. During a week in 50 per cent oxygen he had two minor attacks of upper precordial pain. On discharge his liver was not palpable and his lungs were clear.

One year later he was again admitted. In the intervening year symptoms of precordial pain had continued, brought on by walking one block, accompanied by dyspnea during the preceding three months. Lungs contained subcrepitant râles at both bases. The electrocardiogram now showed auricular fibrillation, T_1 and T_2 upright, S_3 notched. Heart little changed from previous admission. Blood pressure 170/100 mm. of Hg. Liver 3 cm. below costal margin. Blood urea 51 mg. per 100 c.c. He was kept in the oxygen chamber for one week prior to operation and six days after. His postoperative course after thyroidectomy was uneventful. His heart rate returned to sinus rhythm. He returned home three weeks after operation free from pain on mild exercise. Seven months later his electrocardiogram showed sinus rhythm; P_2 notched, S_2 notched, S_3 notched; T_1 and T_2 inverted and T_3 upright. Since the record taken on the previous admission, the T waves in Leads I and II had increased in amplitude and T_3 had become inverted.

His clinical course was characterized by severe facial myxedema which was uncomfortable enough for the patient to require thyroid extract, gr. ¾ daily. When the thyroid dosage was raised to 1 grain daily, walking 15 blocks precipitated an attack of precordial pain for which he went to bed for two days. On his present dose of ¾ gr. thyroid daily, he is able to walk 15 to 20 blocks without pain or dyspnea 16 months after operation. He does not feel strong enough to work. On limited ambulatory activity, he is comfortable. His face appears mildly swollen but



OPERATION: Total Thyroidectomy
DIAGNOSIS: 1. Arteriosclerosis of Coronary Artery
2. Hypertension
3. Cardiac Hypertrophy
4. Fibrosis of Myocardium

CHART 5. Clinical chart showing reduction of pulse rate due to oxygen treatment and elevation of pulse when oxygen was withdrawn.

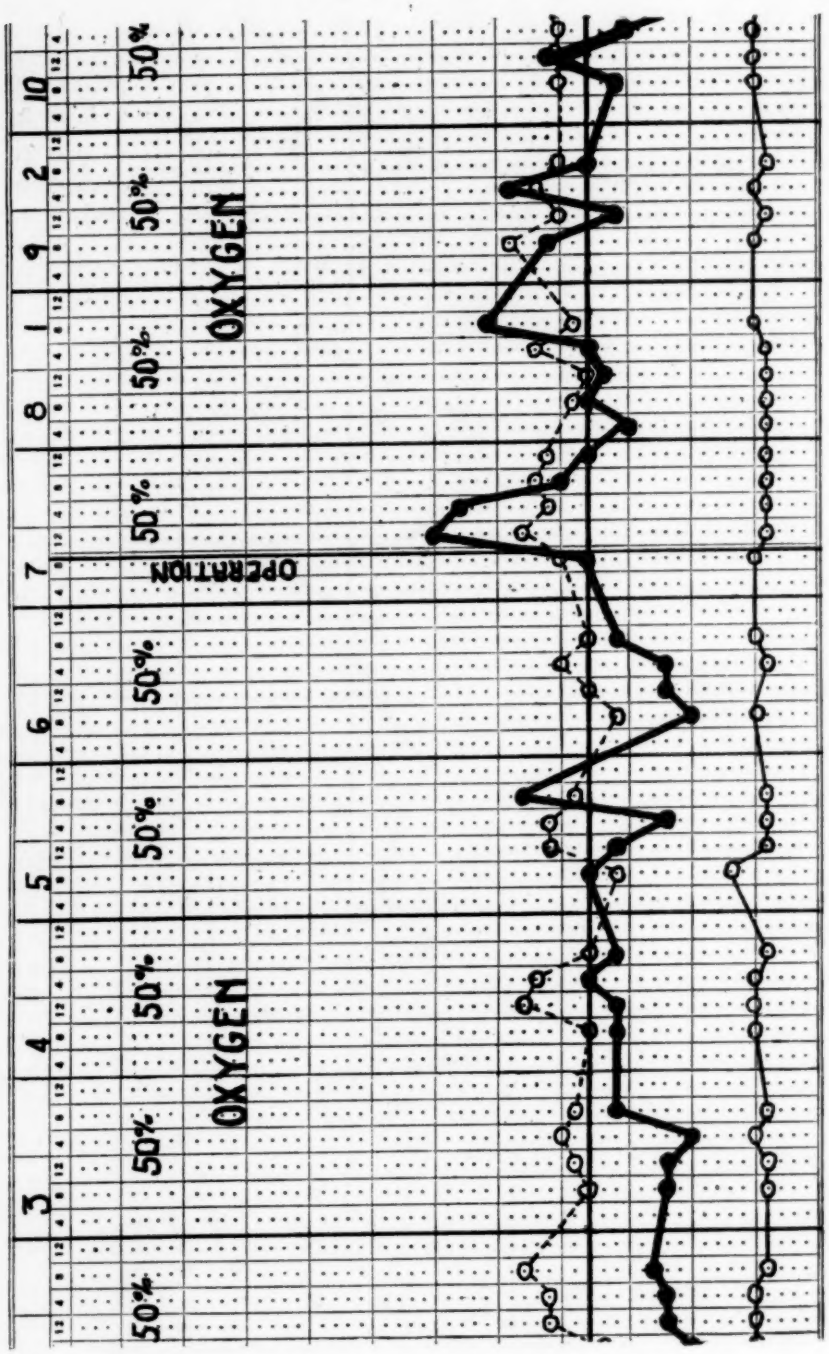


CHART 5—*Continued*

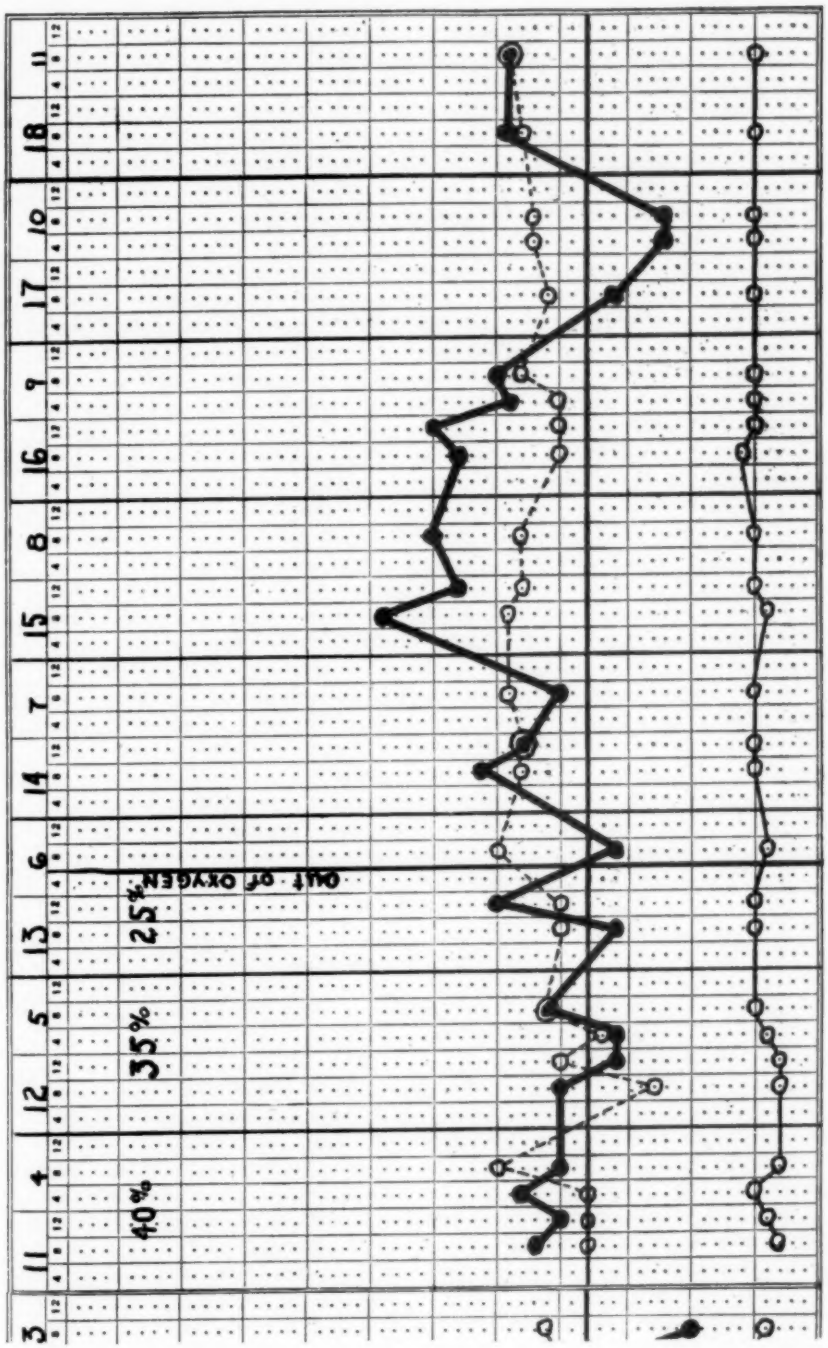


CHART 5—*Continued*

does not distress him. His blood pressure during the first two months after the operation was lower, 145/70 mm. of Hg., but since then it has gradually become more elevated, from 195/125 to 200/130 mm. of Hg. The laboratory data shown in table 6 reveal a slight increase in vital capacity, from 2,000 to 2,650 c.c. The basal metabolism has been kept mainly at minus 35 per cent.

TABLE VI

Case 6	Before Operation	After Operation	Remarks
Date	8-9-34 to 8-21-34	8-21-34 to 10-1-35	
Arterial oxygen saturation	95%	98%	Patient was in oxygen chamber 7 days before and 6 days after operation.
Hemoglobin	118		
Basal metabolism	+3%	−22 to −35%	
R.B.C. millions per cu. mm.	6.8		
Vital capacity	2000	2650	
Blood volume	6180	6780	
Blood velocity	19	11	
Venous pressure	12		
Arterial pressure	180/100	136/58 to 200/130	
Arterial CO_2 vol. per cent	55.2	50.6	
Blood cholesterol		250	
Wt. kg.	66.8	66.4	
Pulse	72	44 to 80	

The patient feels much improved. He is quite philosophic about his inability to work, being content with a life of mild activity, supported by his son. The elevation of his blood pressure, particularly the diastolic, indicates that thyroidectomy has not arrested a pathologic circulatory process. On the other hand, it has made possible a comfortable existence. As a by-product of the operation, the symptoms of intermittent claudication have disappeared.

Case 7. Female, 43 years old.

Past History: Irrelevant. *P. I.:* Patient was well until six months ago when she began to have cough and shortness of breath on exertion. Her symptoms increased until she was confined to bed, one month after the onset of symptoms. In spite of digitalis and complete bed rest, she became progressively worse. Weakness and dyspnea continued with attacks of nocturnal dyspnea for which morphine was used. After four weeks of bed rest she was removed to the hospital and placed in the oxygen room at an oxygen concentration of 50 per cent.

Physical Examination: She was a chronically ill-looking woman sitting propped up in bed, pale without discernible cyanosis. Neck veins were moderately distended. There were dullness and diminished breath sounds and fremitus over the right lower lobe. Heart was enlarged 13 cm. to the left and 5 cm. to the right. A systolic murmur was heard at the apex. There were frequent premature beats. Blood pressure

130/80 mm. of Hg. The liver could be percussed as far as the umbilicus. There was pitting edema over the sacrum and ankles.

Laboratory Findings: Hgb. 90 per cent; r.b.c. 4,500,000; w.b.c. 7,400; polynuclears 76 per cent. Blood N.P.N. 35 mg. per cent. Electrocardiogram showed sinus rhythm; ventricular premature beats; P–R interval 0.16 sec.; left preponderance; P notched in all leads; T_1 and T_2 inverted, T_3 upright. Urine showed a heavy trace of albumin with an occasional hyaline cast. Venous pressure 135.

Course: After entrance to the oxygen chamber the patient had no more attacks of paroxysmal dyspnea, and while at rest breathing was comfortable. She was kept in the oxygen room for three and one-half weeks and then put on nasal oxygen for 10 days. This was gradually reduced from five to one liter per minute before it was discontinued. She lost approximately 15 pounds of edema. She was allowed home and for a period of two months pursued mild ambulatory activities. Then orthopnea, indigestion and slight shortness of breath recurred and she was admitted to the hospital to the oxygen room as a preparation for thyroidectomy. Her vital capacity was 2,000 c.c. Basal metabolism plus 19 per cent. Blood cholesterol 177 mg. per cent. Venous pressure 135. Blood pressure 140/100 mm. of Hg. On examination she had dullness and diminished breath sounds over the right lower lobe and pitting edema over the sacrum. At the end of one week she was again entirely comfortable. She was kept in the chamber for two more weeks, and after she was entirely free from symptoms of decompensation, she was operated on under nasal oxygen and returned to the chamber for one week. She was given oxygen through nasal catheter for one more week, and left the hospital two weeks later. She had a minimal postoperative reaction.

Vital capacity on discharge was 2,800 c.c. Basal metabolism plus 1 per cent four and one-half weeks after operation and minus 8 per cent six months after operation. Venous pressure before discharge, 45.

This patient on her first admission showed a striking improvement on transfer to the oxygen chamber, especially characterized by prompt disappearance of paroxysmal dyspnea. That improvement was not longer maintained seemed unusual in a case of arteriosclerotic heart disease. When she was again put in the oxygen chamber, compensation was rapidly regained. In the six months that have elapsed since operation, she has been very comfortable on mild activity, and says she feels like a new woman. She has appeared definitely to benefit from the thyroidectomy, although the basal metabolism has only been reduced from plus 19 per cent to minus 8 per cent.

An abductor paralysis of both vocal cords has, however, given her a husky voice which has persisted since operation.

Case 8. Female, aged 46.

Family History: Two members of the family have had rheumatism. *Personal History:* Irrelevant. *P. I.:* At age of 33 the patient had her first attack of rheumatism. Six years later she had a second attack at which time she developed cardiac symptoms. For the past three years she has had shortness of breath, orthopnea, rapidly recurring ascites, finally requiring paracentesis every few weeks, frequent hydrothorax and persistent ankle edema.

Physical Examination: A chronically ill negress with edema of ankles and sacrum. Chest shows right hydrothorax and moist râles at both bases. Heart is markedly enlarged both to right and left with signs of mitral stenosis and insufficiency and aortic and tricuspid insufficiency. Blood pressure 120/60 mm. of Hg. Abdomen distended with fluid. Liver down 4 cm. below costal margin.

Laboratory Findings: Hgb. 92 per cent; r.b.c. 5 millions; w.b.c. 8,900; polynuclears, 62 per cent. Venous pressure 278. Vital capacity 750. Serum protein 6.3 per cent. N.P.N. 32 mg. per cent. Electrocardiogram shows auricular fibrillation; left preponderance; R_1 and R_2 notched; T_1 and T_2 isoelectric; T_3 upright.

Course: She was put in the oxygen chamber for one week prior to operation and for three days after operation. She had a minimal postoperative reaction. Basal metabolism plus 5 per cent before operation, minus 23 per cent 23 days after operation, minus 35 per cent eight months after operation. Venous pressure 278 on admission, and 158 twenty-three days after operation. During the following eight months the patient has felt better and able to do definitely more than formerly, but recurring ascites has required paracenteses at intervals of 10 days to three weeks.

Case 9. Male, 60 years old.

Past History: Spontaneous pneumothorax 18 years ago. Questionable history of coronary occlusion 12 years ago. *P. I.:* Hypertension discovered 10 years ago. Four years later he began to have paroxysmal difficulty in breathing at night, gradually increasing in frequency and severity. Three months ago patient had a severe attack of nocturnal dyspnea, and examination at that time showed definite heart failure. Apex rate 90, blood pressure 170/100 mm. of Hg; many premature beats. Liver palpable below the costal margin. Lungs showed moist râles at both bases. Two months ago dyspnea increased, and he complained of severe pain in the left arm. Electrocardiogram showed right bundle branch block, marked slurring and notching of QRS complexes, diphasic T waves and many premature ventricular beats. Blood urea 62 mg. per cent. Basal metabolic rate plus 12.

Physical Examination: The patient showed marked dyspnea, at times gasping. His breathing was distinctly more comfortable while he was in the oxygen chamber (oxygen concentration 50 per cent). He spent 19 days in the chamber, and for 11 days after this was given oxygen by nasal catheter. Thoracenteses were repeatedly necessary, 1,800 c.c. of fluid being aspirated during this period from the right chest. Salyrgan was given at frequent intervals without restoring compensation. The patient was replaced in the oxygen chamber for three days and then operated on, remaining in the oxygen chamber for eight days after operation. He had a slight postoperative reaction.

The vital capacity was 800 to 900 before oxygen treatment, rose to a high of 1,350 before operation and was 1,150 after operation. Venous pressure before operation was 45; velocity of blood flow 45 seconds (Decholin). Salyrgan and thoracenteses continued to be necessary after operation and the patient showed no improvement. Four weeks after the operation, he died of bronchopneumonia.

In this patient with maximal cardiac failure, thyroidectomy appeared to be of no benefit. The progressive nature of the pathologic process was uninterrupted by the attempt made to lessen the work of the heart.

Case 10. Female, aged 65.

Family History and Past History: Irrelevant. *P. I.:* Sixteen years ago, the patient began to suffer from attacks of pain in left arm, shoulder and precordium, at first induced by walking, later by changing from a warm to a cold room, and finally occurring at rest. During the week of admission, she had one severe attack with marked air-hunger and tachycardia.

Physical Examination: The patient was a well-developed, well-nourished woman of 65, sitting quietly in bed, without dyspnea, cyanosis or orthopnea. Her heart was slightly enlarged, and the aortic arch on roentgen-ray appeared to be moderately dilated. No peripheral edema. Blood pressure 200/108 mm. of Hg.

Laboratory Findings: Electrocardiogram: T_1 and T_2 inverted, T_3 upright; left preponderance. Basal metabolism minus 9 per cent. Vital capacity 2,200 c.c. Arterial oxygen saturation 95 per cent.

Course. She was placed in the oxygen chamber for six days before operation and six days after. As indicated by chart 4, her pulse rate was substantially reduced during the period following admission to the oxygen chamber. She had a minimal postoperative reaction. There was an elevation of the pulse rate when oxygen was

discontinued. Three days after leaving the chamber she was anxious to be out of bed. She was discharged, free from pain, one week later. She has been well since operation.

In this patient, freedom from precordial pain was secured following thyroidectomy. Despite her long history and her age, she withstood the operation extremely well. She is in apparently good condition 13 months after the operation, except for the development of severe joint pains having the appearance of chronic arthritis.

Case 11. Male, aged 59.

Family History and Past History: Irrelevant. *P. I.:* Nervousness and dyspnea began two and one-half years ago. A diagnosis of hyperthyroidism was made but the patient refused operation. Since that time, dyspnea has become worse, with increasing palpitation and ankle edema. Two weeks prior to admission, following a sore throat, the patient became orthopneic and was confined to bed.

Physical Examination: Acutely ill man of 59 years, orthopneic and cyanotic, with massive edema of extremities. Thyroid diffusely enlarged. Lungs contained moist râles at both bases. Heart greatly enlarged to left, sounds rapid, systolic murmur at apex. Blood pressure 110/60 mm. of Hg. Liver felt 5 cm. below costal margin.

Laboratory Findings: Hgb. 92 per cent; r.b.c. 5.3 millions; w.b.c. 10,000; polynuclears 74 per cent. Non-protein nitrogen 40 mg. per cent. Venous pressure 265. Electrocardiogram: Auricular fibrillation; left preponderance.

Course. On rest in bed, nasal oxygen, morphine and digitalis he improved rapidly. The basal metabolic rate was found to be plus 50 per cent. On Lugol's solution for one week, the basal metabolic rate dropped to plus 17 per cent. A partial thyroidectomy was performed under the same conditions as in the previous cases, with nasal oxygen and local anesthesia, the patient having been kept in the oxygen chamber for five days before and five days after operation. He had very little postoperative reaction. The basal metabolic rate 18 days after operation was plus 1 per cent. He was discharged, ambulatory and improved. Fibrillation with a slow ventricular rate was present.

This was the only patient in the series in whom a partial thyroidectomy was done. The symptoms of cardiac failure were precipitated by hyperthyroidism and it was felt that reduction to a normal oxygen consumption would be adequate to restore compensation. The smooth postoperative course in this type of case, cardiac failure with hyperthyroidism, was not dissimilar to that seen in the cases of heart disease recited above.

Case 12. Female, aged 30.

Family History: Grandmother had rheumatism. *Past History:* Pneumonia at four years; scarlet fever at six years; no rheumatic fever; chorea at six years. *P. I.:* At the age of 15, patient first noticed palpitation of the heart on exertion, accompanied by shortness of breath. Four years ago increasing dyspnea took place, and one year later she entered the hospital because of cardiac insufficiency. Patient improved but never became free from edema, dyspnea on slight exertion and a swollen abdomen. A second admission became necessary on June 18, 1935, because of increasing orthopnea and swelling of the legs and abdomen.

Physical Examination: A thin, poorly developed negress; moderate orthopnea and dyspnea; doubtful cyanosis. Lungs: Dullness and diminished breath and voice sounds, with moist râles at both bases posteriorly. Heart: Greatly enlarged; dullness at base 8 cm.; in the fourth interspace to the right 5 cm.; 13.5 cm. to the left in the fifth interspace; rhythm totally irregular; systolic and diastolic murmurs at the apex; a diastolic and rough systolic murmur at the aortic area; blood pressure 130/60 mm. of Hg. Abdomen tense and full with a fluid wave; liver palpable at the level of the umbilicus; spleen felt at the costal margin.

Laboratory Findings: Hgb. 75 per cent; r.b.c. 4.2 millions; w.b.c. 8,700; polynuclears 75 per cent. Non-protein nitrogen, 26 mg. per cent; serum protein 5.9 per

cent. Venous pressure 270 to 310. Electrocardiogram: Auricular fibrillation; ventricular rate 50; left preponderance; T_1 upright, T_2 and T_3 inverted. Basal metabolic rate plus 8 per cent.

Course: Patient was treated in the hospital with rest in bed, digitalis and salyrgan for four months, when thyroid ablation was decided upon. At this time her vital capacity was 1,150 c.c.; pulmonary ventilation 6.2 liters per minute; arterial oxygen saturation 91 per cent; circulation time 40 seconds (by sodium cyanide method). Patient was placed in the oxygen chamber for two and one-half weeks prior to operation, which was done under oxygen and local anesthesia. In this patient, the only one of the series, a postoperative reaction took place, the temperature rising to 103.6° F. and pulse from 62 to 96 on the day following the operation, returning to normal on the third day postoperatively. The patient was removed from the oxygen chamber six days after operation.

Four weeks after operation the patient no longer experienced any heart consciousness. However, she began to accumulate fluid in the abdomen again and required salyrgan. The basal metabolic rate at that time was minus 21 per cent.

This patient represents a case of cardiac insufficiency that was not compensated by rest in bed. Although she had a febrile postoperative reaction, the behavior of her heart was at no time embarrassed. The patient did not make any substantial improvement and died six months later of congestive failure.

Discussion of Results

In presenting 12 cases of thyroid ablation in patients suffering from heart disease, we wish to formulate no general conclusions concerning the value of the procedure nor of the special use of oxygen therapy in conjunction with it. Our intention is rather to discuss the results of our experience as a guide to further work in the treatment of cardiac disorders.

That no mortality occurred as a result of operation cannot in such a small series be ascribed to the use of oxygen or to the skill of the surgeon. However, in some instances maximally severe cases of congestive heart failure were chosen, patients who had been bed-ridden five to 18 months, who were brought to an operable stage without manifestations of cardiac insufficiency by residences in a 50 per cent oxygen atmosphere. The severity of congestive failure may be estimated by the marked reduction of the vital capacity in five of our patients who at some time before operation showed the following readings: case 1, 900 c.c.; case 2, 1,100 c.c.; case 8, 750 c.c.; case 9, 800 c.c.; case 12, 1,100 c.c. In the series of Blumgart and his collaborators, the lowest vital capacity among 31 cases tested preoperatively was 1,350 c.c.* In their review of 18 months' experience with thyroid ablation, they report that in 60 cases of congestive failure six have died since operation and six died operative deaths, i.e., within the first three days after operation. Their operative mortality was then 10 per cent. They state that all deaths occurred in patients in congestive failure at the time of operation. Our own series is too small to make statistical comparison with theirs. We wish merely to point out that our interest has centered chiefly in cases in whom compensation in room air under conditions of ambulatory activity could not be obtained, the severity of whose condition is in some instances revealed by the low level of their vital capacities (table 7). We

* Personal communication.

TABLE VII
Summary of Clinical Data in 12 Patients with Cardiac Insufficiency on Whom Thyroid Ablation Was Performed

Case	Age	Sex	Diagnosis	Arterial Oxygen Saturation	Vital Capacity	Venous Pressure	Basal Metabolism	Congestive Failure	Cardiac Pain	Outcome
1	34	F.	Rheumatic valvular heart disease, cardiac insufficiency, ascites	94	900–1100	130–153	−13	4+	0	Marked improvement
2	56	F.	Rheumatic valvular heart disease, cardiac insufficiency, ascites	93	1100–1375	260	− 3	4+	0	Marked improvement
3	22	F.	Rheumatic valvular heart disease, cardiac insufficiency	95	1200–1800	28	−10	3+	0	Moderate improvement
4	51	M.	Arteriosclerosis, coronary sclerosis	92	2400	68	− 2	2+	3+	No improvement
5	51	M.	Arteriosclerosis, coronary sclerosis, aortic stenosis	96	2950	10	+24	0	4+	No improvement; death four months postop.
6	57	M.	Arteriosclerosis, coronary sclerosis, hypertension	95	2000	12	+ 3	1+	3+	Moderate improvement
7	43	F.	Arteriosclerotic heart disease, cardiac insufficiency	—	2000	135	+19	2+	0	Moderate improvement
8	46	F.	Rheumatic valvular heart disease, cardiac insufficiency, ascites	—	750	278	+ 5	4+	0	Moderate improvement
9	61	M.	Arteriosclerosis, coronary sclerosis, hypertension, emphysema, cardiac insufficiency	—	800–900	45	+12	4+	2+	No improvement; death one month postop.
10	65	F.	Arteriosclerotic heart disease, coronary sclerosis	95	2200	—	− 9	0	4+	Moderate improvement
11	59	M.	Hyperthyroid heart, cardiac insufficiency		—	265	+50 to +17	3+	0	Moderate improvement
12	30	F.	Rheumatic valvular heart disease, cardiac insufficiency, ascites	91	1150	310	+ 8	4+	0	Minimal improvement; died 6 months later

wish to draw attention to the fact that preoperative oxygen treatment was employed to increase the efficiency of the circulation, that oxygen was used during and after the operation to prevent anoxemic shock, and finally that under these circumstances there was little or no postoperative reaction, as revealed by the clinical condition of the patients and the charts of their pulse, respiration and temperature. It seemed likely to us, as a result of an experience with an admittedly small number of patients, that the very severe case of congestive failure in whom an operative mortality of some degree might otherwise be expected could with the employment of this program of preparative and postoperative treatment be more safely conducted through the procedure of thyroid ablation. Furthermore, our impulse to utilize thyroidectomy was in the main directed toward this type of case. In two instances, in which prolonged oxygen treatment did not achieve a satisfactory state of compensation, the majority opinion decided against thyroidectomy. In most of the cases, the favorable effect of oxygen treatment was apparent, especially by the lowering of the pulse rate before operation and its elevation when oxygen treatment was discontinued after the operation, examples of which occur in the charts presented. In addition, the scarcity of the symptoms of postoperative reaction impressed us.

The beneficial effect of oxygen therapy immediately following major surgical operations has been reported by Boothby and Haines,[22] Binger, Judd, Moore and Wilder.[23] Judd [24] has already observed, "We feel there can be no question that the use of oxygen postoperatively has a definitely favorable effect on the prevention and treatment of pulmonary edema and congestion. In our opinion, we have materially reduced the incidence of postoperative pneumonia since using oxygen therapy freely following major surgical procedures."

In presenting this communication, we wish to record mainly the clinical data which we observed; the opinions we derived from them are tentative and must await a longer period of trial before we can accept them as established conclusions.

In viewing the results of thyroidectomy itself, we have been especially struck by the improvement in two maximally severe cases of congestive failure, numbers 1 and 2, both due to rheumatic heart disease. In these cases, the change from a bed-ridden existence to one of ambulatory activity was striking and could be distinctly ascribed to thyroid ablation. In neither of the patients was clinical myxedema a troublesome feature. In another case of severe congestive failure, number 8, the time interval has been too short to permit prediction of her ultimate improvement. She is subjectively considerably improved. The vital capacity has increased from 750 c.c. to 1,200 c.c. The venous pressure has fallen from 250 to 97. Paracentesis of the abdomen has been reduced from once a week to once in two weeks. The result in case number 3, one of congestive failure of more

moderate degree than the three above mentioned, is not striking, but it can be safely said that some improvement in the function of her circulation has occurred and that subjectively she is better than prior to operation. The patient whose congestive failure was associated with hyperthyroidism, number 11, is much improved, as might be expected. He was included in the series because he was subjected to the same program of oxygen treatment in association with thyroidectomy. The case of congestive failure, number 9, in whom coronary arteriosclerosis was at the basis of his heart disease, was unimproved, and died one month after operation. His failure was progressive from the time of entrance to the hospital and was uninfluenced by thyroid ablation. The sixth case of congestive failure, number 7, was one of moderate severity. She has been subjectively improved and is able to carry on distinctly increased ambulatory activity since the operation, but the time interval that has elapsed is too small for more to be said than this. The seventh case of congestive failure, number 12, became free from heart consciousness but no substantial improvement took place and the patient died six months later of congestive failure.

There remain four cases in which operation was performed for cardiac pain in the absence of congestive failure. In two, cases 6 and 10, relief from pain was definite, the patients themselves were pleased with the results of the operation and the procedure could be said to have justified itself. The occurrence of severe facial myxedema in one, case 6, ultimately ameliorated by thyroid extract, for a time clouded the patient's satisfaction with the relief of his heart pain. In the remaining two cases, an unsuccessful result was obtained. In one of them, case 4, the patient had a psychoneurosis sufficiently severe as to obscure any benefit he might have received. He did not appear to be subjectively or objectively improved. In the other, case 5, a temporary period of improvement was followed by a progressively severe course ending in death. It should be mentioned in his case that the basal metabolism did not go below minus 20 per cent, and that at autopsy a nodule of hyperplastic thyroid tissue was found. In addition to arteriosclerosis he had a marked aortic stenosis. The other three cases of cardiac pain were presumably cases of coronary arteriosclerosis.

The laboratory data submitted in the tables do not require detailed comment. The blood cholesterol was elevated after thyroidectomy, which is in accord with the careful studies on this point by the original authors.[25] The oxygen saturation of the arterial blood in the cases studied was either slightly lowered or normal. The venous pressure and vital capacity measurements indicate the severity of congestive failure in the individual cases. The blood volume in two cases was reduced after thyroidectomy, suggesting lessened work for the heart. The vital capacity was moderately increased in some cases, although this was not a marked or consistent outcome. The red blood cells tended to show a decrease of a half million to a million cells, with pro-

portionate decrease in hemoglobin, as previously mentioned by Blumgart and his collaborators. The venous pressure was definitely decreased in some patients, uninfluenced in others.

Comment

We are unable to formulate any firm indications for thyroid ablation in the treatment of heart disease; our own experience is too limited and the total lapse of time since the procedure was inaugurated is too brief to permit of final judgment. Nevertheless, we did select the cases that make up the present report with certain principles in mind.

The patient with congestive failure who was bed-ridden all the time, or most of the time, became a potential candidate for thyroidectomy. Also, when the periods of compensation in a patient were very brief, such as a matter of a few months, we regarded these recurring attacks of cardiac insufficiency as indicating a very small cardiac reserve. In other words, the procedure seemed justified when little expectation of comfort could be expected without it.

In the cases with cardiac pain, the existence of unrelieved, severe, frequent pain over the heart raised the question of thyroidectomy. In both groups of cases, the presence of a stationary lesion, rheumatic or arteriosclerotic, increased the indication for operation. Cases that appeared to regain a somewhat stable compensation on oxygen therapy alone were not subjected to thyroidectomy.

We accepted certain contraindications such as a basal metabolism under minus 15 per cent, the presence of nephritis, advanced age—over 75 years —or too youthful an age, such as before puberty. Also, we have avoided choosing patients with syphilitic heart disease, since the pathological process in these cases might be expected to advance despite the production of a lowered oxygen consumption. In addition, we believe the patient should be brought into a state of relative cardiac sufficiency before operation. Oxygen therapy was specially used for this purpose. It was not demanded that these patients should be able to be compensated in room air. Our belief was that if they could be brought to a state of relative cardiac sufficiency in an oxygen chamber, the operation could then be performed with the patients compensated; even if the inhalation of oxygen-enriched atmospheres was necessary for the maintenance of compensation, the fact that the operation was done while oxygen inhalation was still being continued removed the danger of anoxemic shock. It is true that a sudden removal from a high oxygen environment to that of atmospheric air may precipitate cardiac collapse in severely ill patients. However, the method here pursued was to avoid any interruption of oxygen therapy until a safe period following the operation appeared. The subsequent reduction in cardiac work then

allowed the patient to pursue an ambulatory existence without the help of oxygen therapy, as was illustrated by the two severe rheumatic cases of congestive failure in our series.

In the case of angina pectoris, we would now feel doubtful about selecting patients who had such severe coronary artery disease as to suggest an advancing process. The clinical course of these patients is difficult to predict, but in so far as it is possible to do so, the patient with very troublesome pain but with little evidence of progressive coronary disease, would appear a more justifiable candidate than one with very marked and probably advancing coronary changes. In this group, the danger of cardiac failure attending the operation is less real than in the congestive failure patient who is unable to be compensated out of a bed, although postoperative deaths have been reported in this group (Cutler [26]). We adopted a practice of employing oxygen in these cases also, using a smaller preliminary period of treatment. Doubtless, many of these patients would have gone through the operation without reaction. However, anginal pain is itself a result of anoxemia of the heart muscle, and in many cases can be relieved by inhalation of oxygen.[1d] In two of our cases, anginal pain and increased pulse rate recurred four days after the operation when the oxygen concentration of the chamber was lowered and disappeared with elevation of the oxygen concentration. The presence of anemia increases the indication for oxygen treatment in this group.* During a period of stress which an operation induces, the inhalation of oxygen would tend to counteract the development of oxygen debt and therefore tend to maintain the efficiency of the circulation. In patients with anginal pain without congestive failure, the use of oxygen treatment according to the program outlined would therefore appear to be helpful, although not as valuable a procedure as in the patient whose cardiac insufficiency is an immediate problem.

Summary

In 12 patients a program of preoperative, operative and postoperative oxygen treatment has been employed as an adjuvant to ablation of the thyroid gland in cases of heart disease. In patients with congestive failure, their circulation efficiency was improved by the preoperative period of residence in an oxygen chamber. During the operation itself and for a time following it, oxygen therapy tended to prevent the development of oxygen debt and anoxemic shock. Charts showing the effect of oxygen treatment and the absence of severe postoperative reactions have been drawn up. There were no operative deaths.

* Pickering and Wayne [27] reported observations on a series of 25 patients with anemia, eight of whom complained of pain over the sternum induced only by exercise and relieved by rest; in six this pain was no longer experienced after the anemia had been cured, while in two it persisted. The authors concluded from their experiments that the essential factor in the production of anginal pain in anemic patients is a diminished supply of oxygen to the working cardiac muscle and not an inadequate flow of blood.

The physiological effects of oxygen therapy in cardiac decompensation have been reviewed. Its helpfulness in this condition has added further evidence in support of our belief in the value of this form of therapy.

The results of thyroidectomy have been commented upon individually in this study without attempting to formulate firm conclusions. Our interest has been aroused chiefly in severe cases of congestive heart failure of rheumatic etiology in the absence of an active rheumatic process. In two cases of this type followed for a period of over two years, the gain of cardiac efficiency has been striking. The treatment of angina pectoris by thyroidectomy seems to us more wisely restricted to those patients who have troublesome anginal pain in the absence of clinical and electrocardiographic evidence of an advancing sclerosis of the coronary artery. In two cases of this type the clinical betterment which ensued completely justified the operation. Three patients, two with cardiac pain and one with congestive failure and cardiac pain, were not helped. One case of congestive heart failure was not improved and died six months later. The remaining four were improved, the time elapsing since operation being insufficient to permit giving a reliable estimate of the degree of benefit.

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THE THERAPEUTIC ACTION OF THE NUCLEOTIDES; THE TREATMENT OF THE WHOLE BLOOD PICTURE WITH FERROUS ADENYLATE*

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SINCE Rothmann, in 1931, showed that the hemoglobin percentage and the red cell count in a series of patients suffering from widely different diseases bore a fairly constant relationship to the amount of adenylic nucleotide in the blood, there has been a progressively increasing interest in the physiologic rôle of adenylic acid. The *Annual Review of Biochemistry* lists 114 separate papers in one bibliography. In the light of recent investigation, this study has become all the more interesting because of the general enthusiasm which first greeted nucleic acid therapy twenty years ago, and its subsequent failure to materialize. The explanation for this, apparently, lies in the fact that nucleic acid is composed of two groups of nucleotides representing physiologic antagonists in equal amounts and is thus relatively inactive. The prediction of our former teacher, Prof. John Mandel, that the unlocking of nucleic acid would usher in a new era of physiologic chemistry, appears to be approaching realization.

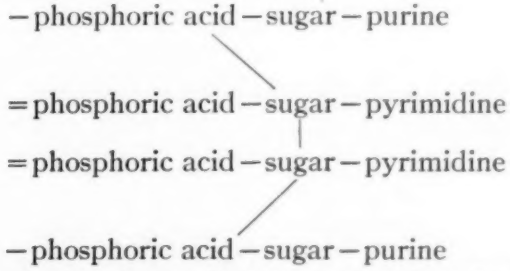
It is well for us to consider, briefly, the formation of nucleic acid before studying the characteristics of the nucleotides which form it.

Nucleic acid when conjugated with albumin or globulin forms a nucleoprotein. As a rule the protein elements may change with the different tissues where the nucleoprotein is formed but the nucleic acid radicles are relatively constant.

Nucleic acid is composed of four nucleotides, two of which are purines, having as the nitrogen containing base adenine and guanine respectively. The other two nucleotides are pyrimidines having the nitrogen containing bases thymine and cytosine. In plant nucleic acid instead of thymine we have uracil.

All four nucleotides have a common structure; thus, the base is united with a glucoside which, in animal nucleic acid is D'ribose, as well as to phosphoric acid.

Thus a picture of nucleic acid, according to Dr. P. A. Levene, is as follows:



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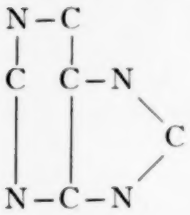
If we group the nucleotides in respect to their physiologic action, we get a schematic arrangement as follows:

ANALYSIS OF NUCLEOTIDE ACTION

NUCLEIC ACID

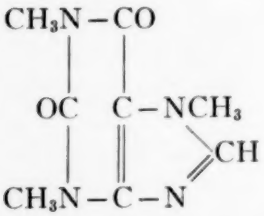
Adenine Nucleotide

Guanine Nucleotide



Purine structure resembling caffeine, etc.

Stimulative



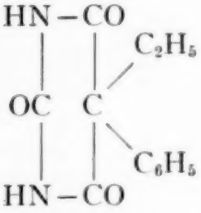
1. Stimulates reticulo-endothelial system, and induces leukocytosis.
2. Increases coronary circulation.
3. Participates in carbohydrate metabolism.
4. Participates in muscle metabolism.
5. Acts as a coenzyme.
6. Is a glandular stimulant.

Cytidilic Nucleotide

Uridylic Nucleotide

Pyrimidine structure resembling phenobarbital

Depressive



1. Precipitates toxins and binds toxalbumin.
2. Induces leukopenia on injection.
3. Inhibits bacterial growth.
4. Is antiseptic in stronger dilutions.
5. Acts like barbiturates on metabolism.

It can therefore be readily seen that, in dealing with the individual nucleotides, we are working with substances radically different from the larger molecule, the nucleic acid. The situation may be considered as analogous to the relationship which coal tar bears to its various physiologically active fractions. This fractionation of nucleic acid has made available a new series of physiologic agents. The isolation of the nucleotides is both costly and difficult; but the value of separating these constituents of nucleic

acid was well pointed out by Doan who states that, " The definite and usually considerable leukocytosis that followed the intravenous injections of relatively large doses (1 gm. of sodium nucleinate), in their series of normal rabbits, was proved to be of unquestionable bone marrow origin. However, a preliminary leukopenia occurred, sometimes lasting for a number of hours before the peripheral leukocytosis was observed, an obviously undesirable phase in the reaction.

It was then determined to see whether this 'active principle,' affecting the myeloid foci in bone marrow, might not be contained in some of the degradation products of nucleic acid, as distinct from the accompanying leukopenia producing factor of the larger molecule. Chemically pure crystalline adenylic and guanylic acid were later tested. These products all gave an immediate neutrophilic response without preliminary leukopenia which recommended them as preferable to the larger nucleinate molecule for clinical use."

Of the four nucleotides, the adenine nucleotide, adenylic acid, has received the greatest amount of attention. Rothmann has shown that there is a direct correlation between the adenine nucleotides and the erythrocyte count and the hemoglobin percentage. This correlation holds in the various conditions ranging from severe anemia to polycythemia. The influence of adenylic acid on the circulation is further shown by the work of De Caro who demonstrated that adenylic acid isolated from yeast nucleic acid (1) lowers the blood pressure, (2) abolishes motility of the intestine, and (3) produces bradycardia. These effects are independent of the sympathetic and para-sympathetic innervation since they are observed in the same degree after the administration of atropine or ergotamine. Similar observations were made by Bennet and Drury whose investigations revealed that adenylic acid is a constituent of many tissues, being found in great amount in striated and heart muscle. It is apparently liberated from injured tissues and may be a contributing factor in inflammations and traumatic shock. The biologic effects of adenylic acid have been found to be identical with those of adenosine, in that (1) the blood pressure is lowered, (2) the vessels of the perfused rabbit lung are constricted, (3) the isolated virgin guinea pig uterus is caused to contract and (4) in that a general leukocytosis may be produced. Drury, furthermore, found that in the perfused rabbit heart, the addition of either guanylic or adenylic acid leads to a brief primary decrease followed by a prolonged increase in the amplitude of the mechanogram. He did not find adenine or guanine to have such influence and concluded, therefore, that the nucleic acid derivatives which contain a phosphoric acid grouping were capable of producing the change.

This is, however, somewhat at variance with the observations of Drury and Weeds on the influence of adenosine in dilating the coronary arteries of the heart. They showed that yeast or muscle adenylic acid have about 66 per cent of the effect of adenosine, whereas inosinic acid, adenine, guanosine,

and sodium nitrate were about 33 per cent as effective as adenosine. Thymus and yeast nucleic acid have an inconstant effect. A slight constriction is occasionally produced. These conclusions are further corroborated by Weld, who found that adenosine caused marked dilation of the coronary vessels, being twenty times as powerful as sodium nitrate. Adenylic acid (yeast or muscle), adenine, or guanosine also dilated the coronary vessels but were not as effective as adenosine.

Among the earlier investigations of the nucleotides, adenylic and guanylic acid, is that of Rosenfeld who found, upon the injection of these acids in the form of the sodium salts, an increase in the uric acid and total nitrogen of the urine. This increase in total nitrogen was greater than the nitrogen contained in the injected substances, while the increase in uric acid was only 10 per cent of the value calculated for the complete conversion of the purine. It is not unlikely, therefore, that the effect on the composition of the urine is explained, in part at least, as due to an increased metabolism and increased glandular activity.

The occurrence of adenylic acid and its isolation from the blood were demonstrated by Hoffman, Jackson, Buell and Perkins. Its presence in and isolation from milk has been proved by Kay, from brain by Pohle, from muscle by Ostern and from kidney by Embden.

How significant a rôle adenylic acid plays in the normal metabolism is gleaned from its relationship to carbohydrate metabolism. The investigations of Myrbock and Euler have shown that cozymase activity is associated with a nucleotide which, in certain respects, resembles muscle adenylic acid. It has not been obtained in crystalline form, nor has a crystalline salt been prepared from it. Studies of the rate of hydrolysis show that this nucleotide belongs to the same group as inosic acid and muscle adenylic acid, but it is clearly distinguished from the adenosine phosphoric acid obtained from yeast nucleic acid.

That adenylic acid plays an important rôle in metabolism is further substantiated by the observations of Lehmann who showed that the esterification with trihydrogen phosphate through the lactic acid enzyme system proceeds only in the presence of adenyl-pyrophosphate plus magnesium. He showed that frog muscle extract loses its ability to hydrolyze glycogen after standing at 20° for two to three hours. Adenyl-pyrophosphate isolated from a fresh muscle can completely restore this lactic acid forming ability to the inoculated extract. Myerhof, Lohmann and Meyer have also demonstrated that the lactic acid forming system of muscle or muscle extracts consists of the thermolabile enzyme and the thermostable coenzyme. The coenzyme must consist of an autolysable and non-autolysable fraction. The former is the adenyl-pyrophosphate. The complement of the coenzyme present in autolyzed boiled juice is the magnesium. Therefore, the magnesium salt must be added besides the adenyl-pyrophosphate to completely

restore its lactic acid forming ability. From these considerations it is concluded that the system,

(1) inorganic phosphate,
(2) adenyl-pyrophosphate,
(3) and the magnesium,

constitutes the coenzyme of lactic acid formation.

Jacobson has in addition shown that an enzyme liberating trihydrogen phosphate from adenyl-pyrophosphate is present abundantly in the liver and to lesser extent in the kidney. Evidence is presented for considering this enzyme as distinct from other phosphatases.

Euler and Myrbock define cozymase as that substance which brings about the typical carbohydrate cleavage in an otherwise inactive mixture of sugar, phosphate, zymphosphate, apozymase, and magnesium salts. They found that the purest preparations of this consisted almost entirely of a substance closely related to adenylic acid (muscle). The close relationship of cozymase to adenylic acid was also demonstrated in an interesting manner by Svengard who showed that injections of cozymase into the jugular vein of rabbits under Wrettan narcosis caused a lowering of blood pressure. This effect was independent of the specific action of the cozymase, since inactivation of the coenzyme by heating did not interfere with the lowering of the blood pressure. Pure adenylic acid of yeast is somewhat more active in this respect, possibly because of the fact that the cozymase is not an entirely pure adenylic acid. The introduction of the thio-methyl group into the adenosine molecule apparently does not diminish this special action. The action of cozymase in lowering the blood pressure is a non-specific effect of the adenylic acid or the homologous adenosine derivatives. This is further corroborated by Zipf in his observations with muscle adenylic acid.

Not only do we find adenylic acid playing an important rôle in carbohydrate metabolism, but it is no less significant in its influence on muscle metabolism. Thus, Schmidt showed that it undergoes enzymic deamination when treated with the pulp or press juice from rabbit muscle. The free purine on the other hand remains practically unaltered when subjected to this treatment. Likewise, Embden and Wassermeyer performed experiments which proved that the source of the ammonia in muscle contraction is from the NH_2 group in adenosine phosphoric acid. The influence of adenylic acid during muscle contraction has been carefully studied by Embden and Lehnartz who found the amounts of free pentose and pentoside in muscle increased following contraction, which indicated that the increased phosphate regularly observed was liberated from an adenylic acid complex. Many authors further suggest that in the recovery period of muscle contraction the pyrophosphoric acid is resynthesized both from the free trihydrogen phosphate and the split off product of adenylic acid. For confirmation, they point to the increase of free pentose during the two hour recovery period of fatigued muscle.

These studies of the purine nucleotides thus reveal the beginning of an analytic break-up of nucleic acid into a series of substances possessing independent properties in balanced systems not yet completely revealed. From the physiologic standpoint the separation of the purine from the pyrimidine nucleotides makes a radical difference in availability; for, the purine nucleotides possess valuable stimulative action on the reticulo-endothelial system and form a valuable vehicle for metal salt therapy while the pyrimidines, because of their depressing action on the reticulo-endothelial system, are undesirable for injection. On the other hand, the increased solubility of the pyrimidines makes them available for salts such as the silver salts, that are used in topical application. The interesting disclosure of Williams, that vitamin B is a pyrimidine thiazole compound, lends added interest to these substances.

One of us, Dr. Simon L. Ruskin, has therefore synthesized all the metal and metalloid salts of adenylic and guanylic acid as well as the metal and metalloid salts of cytidilic and uridylic acids.

In studying these preparations, it is interesting to note that ferrous adenylate provides a non-toxic iron for intramuscular or intravenous use that is stable, readily soluble, and non-irritating on injection, having a pH close to neutral. How valuable the combination of iron with a physiologically occurring radical may be can be seen from Rothmann's study showing that the average value of this nucleotide in blood is from 15 to 18 mg. per cent. He finds that there is a distinct correlation between adenylic acid and the erythrocyte count. In anemia the lowest values are found, in polycythemia the highest. The daily destruction of erythrocytes explains the relatively large amount of adenylic acid excreted in the bile. The injection of this nucleotide leads to a rise in excretion of uric acid in the urine. Rothmann believes that adenylic acid plays an important rôle in the endogenous metabolism of uric acid. Engelhardt regards the adenyl pyro-nucleotide as a component of the coenzyme system of respiration. Thus, in employing ferrous adenylate we have a therapeutic agent in a more potent form not only for stimulating erythrocyte and leukocyte formation, but also for enhancing the respiratory coenzyme system in which the iron also plays a rôle.

In approaching the clinical study of the therapeutic action of the nucleotides, we selected, for this investigation, the influence of the nucleotides on the blood picture, leaving for later study the other aspects discussed in this paper. The relationship between hemoglobin, erythrocyte count and leukopenia has hitherto received but little study. Even though the proverbial tonic has always been directed toward hemoglobin and red cell formation, nevertheless, it appears that the white cell should really be the objective. Roberts and Kracke, in a comprehensive study analyzing the accumulated data in terms of white cell level and symptomatology, reviewed 8000 cases of private clinic patients. One of every four was found to have had a mild granulopenia. One of each two women patients, between the ages of 40 and 60, was neutropenic, and complaints of weakness, exhaustion and

fatigue, with a tendency to sleep, were twice as frequent in the granulopenic individuals as in those showing a normal white cell count. Eighteen per cent of the granulopenic group gave a chief complaint of nervousness. Furthermore, the severity of the symptoms paralleled, to a remarkable extent, the degree of granulopenia found.

In our own cases, cited below, the feeling of well being was far in excess of the rise in hemoglobin and erythrocytes, even though the latter increase was in itself considerable.

The relationship between leukopenia and anemia was further emphasized by Roberts and Kracke who say that, in the attack of pernicious anemia the granulocytes often decrease with the normocytes, and the characteristic granulocytes of pernicious anemia seem to be the first blood evidence of the attack and the last after remission has begun. If one could explain agranulosis, he might also be able to explain pernicious anemia.

The first extensive series of clinical tests was conducted with ferrous adenylate, prepared in half and one grain doses with the assistance of the Merck Research Laboratory. The clinical aspects were carefully followed by one of us, Dr. Elihu Katz, in selected cases. Although over 1,000 injections were administered in a wide variety of patients, no untoward local or general reaction was observed at any time. The case reports present several of those controlled by Dr. Katz (table 1).

Since the ferrous adenylate is the salt which has been selected for clinical trial, it is well to point out several of the factors relative to iron therapy. Since ferrous adenylate is soluble without the addition of ammonium, it is non-irritating and available for intravenous as well as intramuscular use. The Heath, Strauss and Castle report, that the parenteral administration of iron resulted in 100 per cent iron utilization, has established the value of parenteral iron medication and made possible a precise determination of iron need and supply. According to Fullerton, blood iron corresponding to 100 per cent hemoglobin (Haldane scale) is equal to 48 mg. per 100 c.c. Assuming blood volume to be 5 liters, a rise of 1 per cent hemoglobin is equivalent to a gain of 48/100 by 50 equals 24 mg. Fe as hemoglobin. Since a 1 per cent rise of hemoglobin may be considered as a satisfactory result from iron salt therapy, 24 mg. can be considered the essential therapeutic dose. This amount of iron is found in 1½ grains of ferrous adenylate. When one compares this with the oral administration of 90 grains to supply the utilized amount of less than half a grain, one gets a better perspective of the relative merits of oral and parenteral therapy. The discomfort of daily use of large amounts of ferric ammonium citrate may be obviated by the parenteral route.

The immediate hormonal action of the adenylate radical on the circulation was apparent in all of the cases observed. During several hours following the injection, the patients would, as a rule, experience a sensation of exhilaration and a mild flushing of the skin. Several children showed a marked improvement in facial color. One of the patients showed an initial

TABLE I

Case	Age	Sex	Diagnosis	Injections				Comment
				1st, 2nd, 3rd	4th, 5th, 6th	7th, 8th, 9th	10th, 11th, 12th	
No. 1 A.C.	32	F.	Secondary anemia, pyelitis.	Hgb. 58% R.B.C. 3,240,000 W.B.C. 5,300 Hgb. 61% R.B.C. 2,980,000 W.B.C. 5,900 Hgb. 63% R.B.C. 3,200,000 W.B.C. 7,400	70% 3,130,000 7,600 70% 3,250,000 7,600 71% 3,250,000 7,600	73% 3,720,000 7,800 74% 3,340,000 7,500 76% 3,600,000 7,500	77% 4,000,000 7,800 80% 4,000,000 7,800 81% 4,100,000 7,900	After 12 injections of ferrous adenylate and diet, the patient showed marked improvement in the general physical condition. Repeated urinalysis still showed, however, faint traces of albumin and pus cells.
No. 2 R.S.	55	F.	Chronic mitral diseases and secondary anemia.	Hgb. 62% R.B.C. 3,140,000 W.B.C. 4,500 Hgb. 62% R.B.C. 3,200,000 W.B.C. 4,500 Hgb. 63% R.B.C. 3,300,000 W.B.C. 5,000	65% 3,500,000 5,000 65% 3,500,000 5,000 70% 4,000,000 6,200	72% 3,900,000 6,300 75% 4,200,000 8,016 78% 4,500,000 7,200		There was rapid improvement and the patient frequently remarked that she never felt so well in years.
No. 3 C.T.	32	F.	Psychoneurotic.	Hgb. 68% R.B.C. 4,730,000 W.B.C. 7,375 Hgb. 68% R.B.C. 4,700,000 W.B.C. 7,500 Hgb. 68% R.B.C. 4,700,000 W.B.C. 7,000	70% 4,550,000 7,200 72% 4,400,000 7,000 74% 4,800,000 7,500	74% 4,900,000 7,600 76% 4,800,000 8,000 78% 5,000,000 8,900	80% 4,900,000 8,000 81% 5,000,000 8,300 83% 5,000,000 8,500	Patient improved both mentally and physically.
No. 4 S.H.	31	F.	Lacerations of the cervix and vagina; secondary anemia; possible cholecystitis.	Hgb. 75% R.B.C. 3,910,000 W.B.C. 4,088 Hgb. 70% R.B.C. 3,600,000 W.B.C. 4,000 Hgb. 73% R.B.C. 3,640,000 W.B.C. 4,200	75% 3,880,000 5,000 78% 4,000,000 5,600 77% 3,950,000 5,800	79% 3,880,000 6,200 79% 3,900,000 5,000 83% 4,000,000 5,800	85% 3,990,000 4,975 85% 4,000,000 6,000 85% 4,100,000 5,800	No definite diagnosis could be made. Patient improved steadily. Appetite returned. The blood pressure rose from 92 systolic to 110. She was loathe at first to admit improvement but after 12 injections frankly admitted she was better.
No. 5 F.W.	30	F.	Psychoneurotic with secondary anemia.	Hgb. 79% R.B.C. 4,200,000 W.B.C. 5,700 Hgb. 79% R.B.C. 4,250,000 W.B.C. 5,500 Hgb. 82% R.B.C. 4,300,000 W.B.C. 5,600	81% 4,200,000 5,500 80% 4,300,000 5,460 80% 4,200,000 5,500	81% 4,300,000 6,000 83% 4,500,000 6,000 85% 4,300,000 5,940	85% 4,500,000 6,700 86% 4,400,000 6,800 89% 4,500,000 6,866	Patient responded nicely but not as rapidly. Still suffers from insomnia.
No. 6 C.F.	55	M.	Hemorrhoids, secondary anemia.	Hgb. 68% R.B.C. 3,300,000 W.B.C. 6,000 Hgb. 65% R.B.C. 3,000,000 W.B.C. 5,800 Hgb. 68% R.B.C. 3,000,000 W.B.C. 6,000	69% 3,200,000 6,600 73% 3,500,000 6,500 75% 3,600,000 6,500	77% 3,800,000 6,600 78% 4,000,000 7,200 81% 3,800,000 7,000	82% 3,900,000 7,200 83% 3,900,000 7,100 85% 4,200,000 7,200	While receiving the injections was treated locally for hemorrhoids by a rectal specialist. The local condition responded rapidly. Patient felt well.

TABLE I—*Continued*

Case	Age	Sex	Diagnosis	Injections				Comment
				1st, 2nd, 3rd	4th, 5th, 6th	7th, 8th, 9th	10th, 11th, 12th	
No. 7 H.B.	56	M.	Duodenal ulcer.	Hgb. 68% R.B.C. 3,200,000 W.B.C. 6,800 Hgb. 66% R.B.C. 3,000,000 W.B.C. 6,400 Hgb. 68% R.B.C. 3,200,000 W.B.C. 6,800	68% 3,200,000 7,000 70% 3,600,000 7,600 74% 3,800,000 7,400	74% 3,680,000 7,800 81% 4,000,000 6,900 80% 4,000,000 7,100	82% 4,200,000 7,600 87% 4,300,000 7,800 85% 4,200,000 8,600	The occult blood in the stool disappeared. Patient improved. He was on a modified Sippy régime in addition to the ferrous adenylate.
No. 8 E.L.	44	F.	Chronic cholecystitis, secondary anemia, lacerated cervix.	Hgb. 75% R.B.C. 4,200,000 W.B.C. 5,800 Hgb. 74% R.B.C. 4,190,000 W.B.C. 5,700 Hgb. 76% R.B.C. 4,280,000 W.B.C. 5,900	79% 4,300,000 6,200 81% 4,440,000 6,280 80% 4,400,000 6,500	84% 4,500,000 7,200 84% 4,500,000 6,800 86% 4,530,000 7,100	87% 4,500,000 7,000 88% 4,500,000 6,950 87% 4,500,000 7,300	Patient's physical condition improved to such an extent that operative interference was advised.
No. 9 K.R.	48	F.	Gallstones.	Hgb. 79% R.B.C. 3,800,000 W.B.C. 7,300 Hgb. R.B.C. W.B.C. Hgb. 78% R.B.C. 3,600,000 W.B.C. 7,400	 81% 3,800,000 7,600	83% 4,200,000 7,800 87% 4,250,000 7,900	 88% 4,500,000 8,300	Patient was operated upon after the 11th injection because of acute gall-bladder colic. It is interesting to note that she made a speedy convalescence, more so than is usually the case after an acute operation.
No. 10 C.M.	42	F.	Fibrotic uterus.	Hgb. 60% R.B.C. 3,300,000 W.B.C. 6,016 Hgb. 62% R.B.C. 3,000,000 W.B.C. 6,300 Hgb. 60% R.B.C. 3,000,000 W.B.C. 6,500	53% 2,800,000 6,100 64% 3,000,000 6,000 66% 3,200,000 6,800	68% 3,500,000 7,200 70% 3,600,000 6,800 73% 3,400,000 7,100	70% 3,600,000 7,200 72% 3,650,000 7,000 75% 3,800,000 7,800	Patient at first refused operation. After 12th injection felt better and decided to enter hospital. Hysterectomy was performed and patient made rapid and uneventful recovery. On discharge from hospital, hemoglobin rose to 82 per cent, r.b.c. 4,500,000, w.b.c. 7,400.
No. 11 D.S.	54	F.	Climacteric, secondary anemia, colitis.	Hgb. 71% R.B.C. 3,660,000 W.B.C. 3,300 Hgb. 74% R.B.C. 3,550,000 W.B.C. 5,800 Hgb. 75% R.B.C. 3,550,000 W.B.C. 5,700	77% 4,070,000 4,300 77% 4,030,000 4,400 77% 4,070,000 4,300	70% 3,390,000 5,500 77% 3,740,000 5,500 75% 3,800,000 5,000	77% 3,680,000 5,200 74% 3,920,000 5,000 77% 3,900,000 5,200	General and steady improvement. Menstruated for first time in 10 years after the injections.
No. 12 J.F.	36	F.	Bronchopneumonia.	Hgb. 54% R.B.C. 3,200,000 W.B.C. 11,000			15th Injection 90% 5,200,000 9,000	Rapid return of blood picture with unusual recovery of physical vigor. Case of Dr. M. Silberstein.
No. 13 M.M.	21	F.	Secondary anemia.	Hgb. 60% R.B.C. 3,225,000 W.B.C. 6,200			81% 4,100,000 7,700	Marked improvement in energy, able to resume work efficiently. Case of Dr. Sidney F. Friedman.

TABLE I—*Continued*

Case	Age	Sex	Diagnosis	1st Injection	15th Injection	Comment
No. 14 K.	62	F.	Post pneumonia debility.	Hgb. 45% R.B.C. 2,900,000 W.B.C. 5,200	69% 3,750,000 6,300	Patient felt stronger, appeared fairly ruddy compared to extreme pallor at onset. Case of Dr. Sidney T. Friedman.
No. 15 E.A.	5½	M.	Pan sinusitis.	Hgb. 75% R.B.C. 4,050,000 W.B.C. 7,350	8th Injection 98% 4,390,000 8,350	Nervousness and irritability disappeared, patient ate better. Lost pasty look and pallor. Case of Dr. Sidney T. Friedman.
No. 16	60	M.	Asthma, debility, anemic pallor.	Hgb. 54% R.B.C. 4,600,000 W.B.C. 7,200	10th Injection 80% R.B.C. 4,800,000 W.B.C. 9,400	Subjectively much improved not only from general debility but also from asthma. Was more comfortable.
No. 17	32	F.	Pregnancy 3 months. Miscarriage.	Hgb. 45% R.B.C. 2,800,000 W.B.C. 6,200	12th Injection 80% 4,200,000 8,000	General condition very much improved.

drop in blood pressure with slight sweating and vertigo. Some of the patients had slight tingling sensation in the extremities. The sensation of well being and feeling of increased energy were in excess of those ordinarily experienced from iron therapy alone.

Another noteworthy point was the fact that, although one and one-half grains of ferrous adenylate was the calculated amount of daily iron needed, nevertheless, the dosage employed on the reported cases was only one-half grain of ferrous adenylate. This, in terms of iron alone, would represent only 6 mg. The pronounced hemoglobin response is definitely out of all proportion to this quantity of iron and must represent the supporting action of the adenylic acid, either through its stimulation of the bone marrow, directly, or the improvement of the utilization of iron in the food. In this respect adenylic acid may be looked upon as one of the effective substances so stimulating to blood regeneration found in the various tissue extracts, such as liver, beef, and stomach. There are many factors pointing to this. First, that these tissues are a rich source of adenylic acid; second, that Williams has shown vitamin B to have a pyrimidine nucleus, thus relating this to the adenylic acid structure; and third, the findings of P. Karrer and H. V. Euler, who showed in their paper, on the water soluble growth vitamins of the B group, that the active substance obtained through the physical and chemical treatment of an aqueous liver extract showed spectroscopically a maximum absorption band at 260 mm. which agreed with that of cozymase and the adenyl nucleotide. When one adds to this the findings of Rothmann, that the hemoglobin per cent and erythrocyte count bear a direct relationship to the amount of adenylic acid of the blood, one gets a striking view of the important relationship of the adenylic nucleotide to blood formation.

It is now commonly accepted, as shown by Bethell, "that the retarded rate of hemoglobin formation is most often due to a lack of iron, although such deficiency may possibly be associated with insufficient available protein, pigment complex, and certain vitamins."

Minot has strongly pointed out "that the term iron deficiency does not adequately describe all cases placed under this heading. The withdrawal from the tissues of material to make hemoglobin, the influence of substances on physiologic mechanisms for the utilization of iron and hemoglobin building substances must be studied further before there is final knowledge concerning iron deficiency anemias."

It thus becomes apparent that the use of simple iron compounds such as ferrous sulphate, ferric ammonium citrate, or reduced iron, such as have been used as far back as antiquity, may now be supplanted by the iron compounds of physiologically related radicals and supplemented specific active agents.

The stimulation of bone marrow function, by the continued action of iron and nucleotide, was demonstrated in our cases by the elevation of the whole blood picture in every instance. The feeling of well being experienced by the patient could be compared with the sensation produced by the physiologic leukocytosis following ingestion of food, stimulation of a cold shower or massage. Also, the elevation of a white cell count from three thousand to five or six thousand lessens the danger of approach to the more malignant forms of neutropenia.

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HEPATIC COMPLICATIONS IN THE TREATMENT OF SYPHILIS

II. INCIDENCE OF HEPATIC DISEASE IN PATIENTS WITH UNTREATED SYPHILIS AND DURING THEIR SUBSEQUENT TREATMENT *

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Hepatitis as a complication of anti-syphilitic therapy is not an uncommon occurrence. The injury thus suffered by the liver may be transient or it may be permanent, resulting in cirrhosis. Thus Baldridge [1] reported that, of a series of 36 patients with definite portal cirrhosis, one-third had histories of treatment for syphilis. During the past 10 years the value of controlling the arsphenamine treatment of syphilis by functional tests of the liver has been repeatedly emphasized. Such tests are indicated especially for patients with histories of hepatic disease or with evidence of disturbance of the liver developing during the course of treatment. Previous studies [2] have also shown that liver-function tests may reveal hepatic disease in a number of patients who present no clinical signs of liver dysfunction.

Consequently, it seemed desirable to survey a group of patients with untreated syphilis, and to follow these patients with repeated functional tests of the liver during their subsequent treatment. In this way it was hoped to determine: (1) the incidence of hepatic disease in patients with untreated syphilis; (2) the effect of anti-syphilitic treatment on the liver; and (3) the possible relationship of diminished liver-function to untoward reactions resulting from treatment.

Method of Study. The patients with syphilis who were selected for this study had received little or no antisyphilitic treatment. Some of these patients had received a few treatments with bismuth or mercury and a few had received one or two treatments with an arsphenamine. Thorough physical examinations were done on all patients, and complete histories were taken with special reference to antecedent disease of the liver. The liver-function of these patients was checked routinely with the Rose Bengal dye test at the onset of treatment, and at intervals during the course of therapy. This test has been used in the University of California Hospital the past 12 years, and has proved a reliable and satisfactory method of determining hepatic function. Details of the technic have been recently described,[3] and will not be repeated here. A retention of over 55 per cent of the dye in the blood stream at the end of eight minutes, and of over 35 per cent of the dye at the end of 16 minutes, is considered to indicate abnormal hepatic func-

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tion. For the purposes of this study more stringent criteria were selected, and only patients with a retention of the dye of over 60 per cent at the end of eight minutes, and of over 40 per cent at the end of 16 minutes were considered to have abnormal hepatic function.

Some of the patients with abnormal hepatic function were further tested for disease of the liver by the modified glucose tolerance test,[4] and by determination of urobilin in the urine.

Observations. A total of 90 patients, on whom a total of 200 Rose Bengal tests were performed, was studied. Unfortunately a large percentage of patients treated at this clinic are transient, so there were 39 patients on each of whom we were able to make only one test. The remaining 51 patients had two to six tests each during the course of their treatment.

Of the entire group, 57 were males and 33 were females. The age distribution, shown in table 1, indicates that the greater number were between

TABLE I

Distribution of Patients According to Age and Sex

Entire Series							
Age	10–19	20–29	30–39	40–49	50–59	60–69	Total
Male	3	17	14	17	5	1	57
Female	2	9	10	7	4	1	33
Total	5	26	24	24	9	2	90
Group with Abnormal Hepatic Function before Treatment							
Male	0	1	2	8	3	0	14
Female	0	0	4	1	0	1	6
Total	0	1	6	9	3	1	20

20 and 50 years of age. When grouped according to the diagnosis made at entry, 15 were in the primary stage, 23 were in the secondary stage, 35 were classified as latent, and 17 were classified as late—four of these latter having syphilis of the central nervous system.

The incidence of abnormal liver function as indicated by the Rose Bengal test was surprisingly high. Of the 90 patients in our series, 20 had abnormal liver-function before antisyphilitic treatment was given. As shown in table 1, there was a tendency for this group to be of an older age than the group as a whole, but there was no definite correlation between the liver-function and the stage of the disease in these patients.

Group with Repeated Tests; Normal Liver Function before Treatment. Of the patients with normal hepatic function before antisyphilitic treatment, 33 had repeated tests during the course of therapy. Five of these (table 2) were shown to have an abnormal test of liver-function while under treatment. In two patients (numbers 2 and 5), the hepatic function was still

TABLE II

Patients Developing an Abnormal Retention of Rose Bengal Dye during the Course of Antisyphilitic Therapy

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Preceding Arsenical Treatment	Remarks
					8 min.	16 min.			
1	34	M	Latent syphilis	4–12–34	42	20	None	None	Urobilin absent in urine 5–10–35
				10–13–34	72	40	Slight	Neoarsph. 4.5 gm.	
				5–10–35	64	32	None	Neoarsph. 9.0 gm.	
2	29	M	Tabes dorsalis	10–22–33	60	27	None	Neoarsph. 1.3 gm.	Moderate alcoholic history
				3– 2–34	69	41	Slight	Neoarsph. 4.0 gm.	
				7–14–34	32	24	None	Neoarsph. 45 gm.	
				6–17–35	72	37	Slight	Tryparsamide 38 gm.	
3	45	F	Latent syphilis	9– 3–34	51	28	None	None	Malaise following second treatment of neoarsphenamine. Urobilin absent in urine 5–6–35. Modified glucose tolerance test indicative of hepatic damage 6–5–35
				2– 8–35	62	40	Slight	Neoarsph. 3.5 gm.	
				5– 6–35	56	32	None	Neoarsph. 0.9 gm.	
4	41	M	Primary syphilis	3– 7–34	48	24	None	Maphars. 0.09 gm.	Moderate alcoholic history. Mild hepatitis and glomerular nephritis while on therapy with bismuth 9–10–34. Tolerated further treatment without reaction. Urobilin present in urine 5–13–35
				7–28–34	68	46	Moderate	Maphars. 0.9 gm.	
				10–13–34	54	28	None	None	
				5–13–35	56	26	None	Maphars. 0.95 gm.	
5	64	M	Latent syphilis	5–29–34		30	None	None	Urobilin absent in urine 5–6–35
				9–24–34	88	53	Moderate	Maphars. 0.40 gm.	
				5– 6–35	67	43	Slight	Maphars. 0.60 gm.	

abnormal at the time of the last examination, antisyphilitic treatment apparently having led to permanent hepatic damage. In the other three patients the abnormality was transient, and subsequent arsphenamine therapy was tolerated without mishap, though one patient (number 4) had had an attack of jaundice and glomerular nephritis.

Group with Repeated Tests; Abnormal Hepatic Function before Treatment. There were 18 patients in this group, which can suitably be divided into a sub-group of 9 (table 3) in whom the function returned to normal following antisyphilitic therapy; and the remaining 9 (table 4) in whom the function of the liver continued to be abnormal.

In table 3 we have included a group of patients who may have had syphilitic involvement of the liver, inasmuch as the hepatic function improved with antisyphilitic therapy, although one patient (number 6) showed further impairment of liver-function before improvement occurred. Three patients (numbers 6, 9 and 11) had transitory attacks of dermatitis, probably related to antisyphilitic therapy. In one patient (number 8), an abnormal reading was obtained when the Rose Bengal test was performed a few hours after an injection of neoarsphenamine. This may represent only a temporary toxic effect on the liver, for in the course of our study on other patients a similar relationship has not infrequently been noted.

Table 4 represents a group of patients with an abnormal hepatic function which persisted after a period of one to two years of antisyphilitic treatment. It is highly significant that an increased impairment of hepatic function occurred in four (numbers 19, 20, 21, and 22) of this group during the course of arsphenamine therapy. In one patient (number 19) who had developed icterus, a marked improvement in liver-function followed the cessation of arsenical treatment. One patient (number 22) developed purpura after each administration of neoarsphenamine but tolerated mapharsen without ill effect.

Group with Only One Rose Bengal Test. As stated before, there were 39 patients on whom only one Rose Bengal test was done. No reactions to arsphenamine therapy occurred in these patients while attending the clinic. Two patients (table 5) had definitely abnormal hepatic function. One of these (number 24) had a decompensated cirrhosis of the liver. This patient was lost sight of before antisyphilitic treatment was given.

Relation of Abnormal Hepatic Function to Untoward Reactions of Therapy. Eighty patients received treatment with the arsphenamines. Sixty-two of these patients had initially a normal liver-function, and 18 had abnormal function.

Table 6 shows the untoward reactions which occurred. Approximately one-fifth (12 patients) of the group with initial normal function manifested some degree of intolerance to arsenic at one time or another. The only serious reaction occurring was the jaundice and glomerular nephritis which one patient developed. Subsequently, this patient tolerated arsenical therapy without untoward effects.

TABLE III

Patients with Abnormal Retention of Rose Bengal Dye Initially, but with Normal Function following Specific Therapy

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Preceding Arsenical Treatment	Remarks
					8 min.	16 min.			
6	45	M	Secondary syphilis	5– 1–33	62	38	Slight	Neoarsph. 1.2 gm.	Several attacks of dermatitis questionably related to therapy. Modified glucose tolerance test indicative of hepatic damage 7–26–33
				6–26–33	76	52	Moderate	Neoarsph. 3.4 gm.	
				10–25–33	62	38	Slight	Neoarsph. 3.3 gm.	
				6–18–34		24	None	Neoarsph. 4.7 gm.	
7	44	M	Latent syphilis	4–17–34	66	43	Slight	None	Slight alcoholic history. Icterus index 7 on 5–13–35. Urobilin absent in urine 5–13–35
				5–13–35	57	29	None	Maphars. 0.92 gm.	
8	21	M	Secondary syphilis	5–29–33	70	40	Slight	Neoarsph. 0.45 gm.	Rose bengal test performed 4 hours after first treatment with neoarsph.
				7–24–33	46	20	None	Neoarsph. 3.5 gm.	
9	52	M	Late syphilis	5–22–33	68	43	Slight	None	Dermatitis questionably related to therapy with bismuth. Urobilin present in urine 5–22–33 and 5–3–35
				8–21–33	67	34	None	None	
				10– 2–33	53	29	None	None	
				10– 4–34	65	43	Slight	None	
				5– 3–35	56	33	None	Neoarsph. 3.1 gm.	
10	33	F	Primary syphilis	8–13–34	68	43	Slight	Maphars. 0.11 gm.	Icterus index 6 on 6–28–35
				2–25–35	63	35	Slight	Maphars. 0.55 gm.	
				6–28–35	52	24	None	Maphars. 0.36 gm.	
11	49	M	Latent syphilis	3–28–34	70	40	Slight	None	Transient dermatitis following neoarsph. 12–15–34
				10–22–34	59	35	None	Neoarsph. 1.1 gm.	
				3–18–35	66	34	None	Neoarsph. 4.7 gm.	

TABLE III—*Continued*

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Preceding Arsenical Treatment	Remarks
					8 min.	16 min.			
12	43	M	Latent syphilis	1–17–34	64	46	Moderate	None	Liver slightly enlarged. Modified glucose tolerance test indicative of hepatic damage 6–17–35
				4–16–34	68	44	Moderate	None	
				9–28–34	57	37	Slight	Neoarsph. 3.5 gm.	
				2– 8–35	62	40	Slight	Neoarsph. 4.8 gm.	
				4– 1–35	56	34	None	Neoarsph. 4.7 gm.	
13	47	M	Latent syphilis	1– 8–34	80	48	Moderate	None	
				3– 7–34	52	28	None	Neoarsph. 0.3 gm.	
				10– 1–34	76	35	Slight	Neoarsph. 3.5 gm.	
				2–25–35	56	33	None	Neoarsph. 4.5 gm.	
14	32	F	Latent syphilis	6–12–33	61	36	Slight	None	Urobilin present in urine 8–9–35
				2–18–35	64	41	Slight	Neoarsph. 10.0 gm.	
				8– 9–35	56	30	None	Maphars. 0.32 gm.	
15	35	M	Recurrent secondary syphilis	4– 4–34	58	38	Slight	None	Strong alcoholic history. Liver slightly enlarged
				2–18–35	66	40	Slight	Neoarsph. 9.0 gm.	
				8–20–35	54	27	None	Neoarsph. 4.0 gm.	

TABLE IV

Patients with Initial Abnormal Liver Function Which Is Unaltered or Made Worse by Antisyphilitic Therapy

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Preceding Arsenical Treatment	Remarks
					8 min.	16 min.			
16	41	M	Secondary syphilis	5–15–33	60	36	Slight	Neoarsph. 0.9 gm.	Slight alcoholic history. Catarrhal jaundice in 1928. Icterus index 11 on 8–2–33. Urobilin absent in urine 5–3–35
				10–24–33	56	34	None	Neoarsph. 5.4 gm.	
				9–28–34	63	40	Slight	Neoarsph. 11.7 gm.	
				5– 3–35	70	35	Slight	Neoarsph. 4.6 gm.	
17	66	F	Latent syphilis	3– 2–34	64	40	Slight	None	Modified glucose tolerance test indicative of hepatic damage 6–17–35
				10– 4–34	55	37	Slight	None	
				3–11–35	57	34	None	Neoarsph. 2.1 gm.	
				6–14–35	60	42	Slight	None	
18	38	F	Primary syphilis	4–24–34	78	50	Moderate	None	Malaise following first treatment of mapharsen
				2–26–35	76	44	Slight	Maphars. 0.76 gm.	
19	44	M	Latent syphilis, cirrhosis	6–26–33	76	52	Moderate	None	Moderate alcoholic history. Slightly enlarged liver. Urobilin present in urine 6–26–33. Modified glucose tolerace test indicative of hepatic damage 7–26–33. Icterus present October 1934 to March 1935
				7–24–33	83	57	Marked	None	
				11–21–33	71	48	Moderate	None	
				10– 4–34	91	77	Marked	Neoarsph. 3.6 gm.	
				3– 1–35	80	60	Marked	Neoarsph. 4.6 gm.	
				6–18–35	60	44	Slight	None	

TABLE IV—*Continued*

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal .8 min.	Rose Bengal 16 min.	Degree of Abnormality	Preceding Arsenical Treatment	Remarks
20	33	M	Recurrent secondary syphilis	3– 2–34	60	36	Slight	None	Urobilin present in urine 5–3–35
				4–24–34	56	34	None	Maphars. 0.31 gm.	
				5– 3–35	76	50	Moderate	Neoarsph. 4.0 gm.	
21	50	M	Latent syphilis	4–24–34	60	40	Slight	None	Received neoarsphenamine 4 hours before Rose Bengal test 2–1–35
				10– 8–34	59	39	Slight	Neoarsph. 3.5 gm.	
				2– 1–35	80	60	Marked	Neoarsph. 4.0 gm.	
22	48	F	Syphilis of the C.N.S.	6–26–33	69	40	Slight	None	Nausea following first treatment with neoarsphenamine. Subcutaneous ecchymoses following all subsequent treatments of neoarsphenamine. No reaction to mapharsen. Urobilin absent in urine 5–6–35. Modified glucose tolerance test indicative of hepatic damage on 7–6–33 and 6–5–35
					67	34	Slight	Neoarsph. 1.0 gm.	
					63	47	Moderate	Neoarsph. 0.15 gm. Mapharsen 0.26 gm.	
23	59	M	Latent syphilis	2–20–34	80	42	Moderate	None	No arsenical treatment. Received bismuth and mercury
				8– 9–35	88	56	Marked	None	

TABLE V

Patients with Abnormal Initial Hepatic Function, Subsequent Rose Bengal Tests not Performed

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Preceding Arsenical Treatment	Remarks
					8 min.	16 min.			
24	39	F	Latent syphilis, cirrhosis	10–24–33	78	68	Marked	None	Strong alcoholic history. Abdominal distress for 4 years. Edema of ankles and slight icterus for 3 months. Liver greatly enlarged. No arsenical treatment
25	44	M	Secondary syphilis	8–13–34	78	38	Slight	Maphars. 0.10 gm.	Received mapharsen 1.44 gm. without reaction

TABLE VI

Reactions during Course of Antisyphilitic Therapy

	Abnormal Rose Bengal Test before Treatment		Normal Rose Bengal Test before Treatment		Total	
Total number receiving the arsphenamines	18		62		80	
Reactions:						
Dermatitis (mild)	3		4		7	
Malaise	2	7	7	12	9	19
Jaundice	1		1		2	
Purpura	1		0		1	
Enlarged liver before treatment	3		7		10	

Seven (approximately one-third) of the group with initial abnormal function developed untoward reactions. Two had serious reactions, one having jaundice and the other purpura. Although the series is not large enough to be statistically significant, it would appear that patients with abnormal hepatic function are more apt to develop untoward reactions than are patients with normally functioning livers.

Comment. The findings presented demonstrate that latent hepatic disease is not uncommon in patients with untreated syphilis. Of the entire series of 90 patients, 20 were found to have abnormal liver-function as shown by protracted retention of Rose Bengal dye in the circulation. Two of these patients had other clinical evidence indicative of cirrhosis of the liver, and a third patient had a history of jaundice. The remainder, 17 in number, had impaired liver-function which was detected only by the Rose Bengal test. In 10 of these 17 patients improvement in hepatic function followed specific therapy, while in the remaining seven, the liver-function remained abnormal in spite of long continued antisyphilitic therapy. Improvement in the patient's syphilitic condition probably accounts for the improvement in the liver-function in the first 10 while in the other seven the liver disease was probably so advanced that the function could not be restored. It is in this group where extreme caution must be exercised in the administration of the arsphenamines as irreparable harm may be done by these drugs.

Only one patient (table 4, number 19) with clinically recognizable cirrhosis of the liver received arsenical therapy. This was tolerated poorly, and jaundice developed which subsequently disappeared only after treatment with arsphenamine was discontinued. The patient (table 4, number 16) with a history of jaundice suffered no untoward effects from treatment. Six of the seven patients with presumably latent cirrhosis were given the arsphenamines cautiously. This was well tolerated except for one patient (table 4, number 22) who developed purpura following neoarsphenamine. In two other patients (table 4, numbers 20 and 21), antisyphilitic therapy led to increased hepatic damage as shown by the Rose Bengal test.

Of the 29 patients with an initial normal hepatic function test, five developed hepatic injury as shown by the Rose Bengal test. This damage was slight to moderate, and relatively transient. One patient (table 2, number 4) developed jaundice and glomerular nephritis temporarily, but subsequently tolerated arsenical treatment without reaction. Since the development of cirrhosis is a relatively slow process, a further study of these patients is indicated to determine the possible relationship of antisyphilitic therapy to the future course and end result.

An analysis of the untoward reactions occurring during antisyphilitic therapy suggests that patients with an abnormal hepatic function are more apt to suffer ill effects than those with normal liver-function. If this is borne out by further observations, it would be advisable to perform routine liver-function tests on all patients with syphilis before instituting therapy. Every effort should be exerted to protect the liver from the harmful effects of antisyphilitic remedies. We would suggest the taking of carbohydrates by mouth a few hours before the administration of an injection of arsphenamine and caution the patient against the taking of alcohol or an excess of fat in his diet.

Summary

1. A high incidence (19 per cent) of abnormal liver-function, as shown by the Rose Bengal test, was found in a group of 90 patients with untreated syphilis.

2. Antisyphilitic therapy caused transitory disturbances in liver-function in five of 29 patients originally having a normal function; and caused further impairment in four of 18 patients with initial abnormal function.

3. Patients with initially abnormal liver-function had an increased tendency to have untoward reactions to antisyphilitic therapy.

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NEUROLOGICAL SYMPTOMS IN POSTHEMORRHAGIC SECONDARY ANEMIA *

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IN 1878 the pathological picture of postero-lateral-sclerosis was described by Kahler and Pick,[1] and in 1887 Lichtheim [2] pointed out the frequency of the relationship of this neurological condition to pernicious anemia. At the present time the symptom complex of postero-lateral-sclerosis is regarded as most commonly the result of primary pernicious anemia. The relationship of secondary anemias to changes in the nervous system, however, is less well known. Changes in the cord occurring in secondary anemia have been reported, but not all these cases can be accepted as authentic.

Oppenheim [3] believed that in all cases of postero-lateral-sclerosis the anemia need not be pernicious, and he reports one case in which the postero-lateral-sclerosis was the result of the cachexia due to a malignant tumor, one occurring during the anemia of lactation, and three cases in persons in the sixth and seventh decade of life who had an anemia he attributed to chronic malaria which was contracted in early life. These cases were reported before our present knowledge of pernicious anemia and cannot be accepted as due to secondary anemia without question, although many German neurologists in the past have likewise held the opinion that secondary anemia may cause changes in the nervous system.

Sargant [4] reports cases of simple achlorhydric anemia where symptoms of postero-lateral-sclerosis existed and in whom marked improvement of both the blood picture and nervous symptoms occurred from the use of iron, but not from liver therapy. This worker believes that in all types of anemia, including pernicious, the nervous symptoms are more promptly and effectively improved by massive doses of iron than by liver therapy alone. All of his cases received at least 150 grains of Blaud's mass each day.

The view that the anemia is not the main factor in the production of the postero-lateral-sclerosis of primary pernicious anemia is based upon the fact that many times the nervous symptoms long precede the anemia. Spiller [5] has long held this opinion. Castle [6] states that pernicious anemia is the result of the absence of a specific intrinsic factor of gastric origin. Nervous system symptoms associated with achylia gastrica are not infrequent, notably in pellagra. In tapeworm and hookworm anemias, and in the anemia of sprue nervous system symptoms are encountered, but they may be the result of the toxic factors of the disease and not due to blood impoverishment alone.

In many of the dietary deficiency diseases there is an associated anemia with nervous symptoms, but the magnificent work of Mellanby [7] tends to prove that here again the anemia cannot be considered the important factor.

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In all his experimental animals he could demonstrate diminution or depletion of the vitamin A content of the liver, and by the addition of vitamin A or carotin to the diet he was able to prevent degenerative changes in the nervous system. It is of interest that in some cases of postero-lateral-sclerosis of pernicious anemia in humans he found decrease in the amount of vitamin A in the liver. This was not a constant finding, but even the presence of vitamin A in the body does not rule out its faulty utilization.

Weil and Davidson,[8] in their exhaustive pathological studies on the spinal cord in anemia, concluded that postero-lateral-sclerosis probably never occurs in any secondary anemia. In their series of cases of secondary anemia, changes in the cord were noticed in a few in which the differentiation between primary and secondary anemia was not clear. They do not consider any other changes in the central nervous system than cord changes and include in their group of secondary anemia all cases with 75 per cent hemoglobin or less and 3,500,000 red blood cells or less. In only eight of their cases of secondary anemia, not including the four leukemias, was the red blood cell count under 2,500,000, and in only six cases was the hemoglobin under 50 per cent. In one of these cases involvement of the column of Goll was noted in a patient who died of tuberculous meningitis. The hemoglobin in this case was 28 per cent. In their cases of secondary anemia which showed central nervous system lesions, these lesions were usually the result of metastatic or myelitic lesions. In this paper of Weil and Davidson the number of really severe cases of secondary anemia is too few to warrant their conclusion that cord changes do not occur in secondary anemia. In the 10 cases of primary pernicious anemia used in their paper, in only two was the hemoglobin above 50 per cent or the red blood cell count above two million, so that aside from the toxic factor their pernicious anemia cases represented much more severe red blood cell and hemoglobin deficiency than their secondary anemia cases.

The cases of anemia with nervous symptoms which I present in this paper are very severe cases, in which there was rapid diminution of the hemoglobin and red blood cells by massive hemorrhage from medical or obstetrical causes to almost fatal levels.

Case Reports

Case 1. The first case was from my service at the Episcopal Hospital. Briefly, the patient, a woman, aged 40, suffered from severe postpartum hemorrhage March 1, 1927. She was in a stuporous state for several days following delivery and complained of blindness and a cold, numb feeling of the body, especially in her lower extremities. It was several weeks before her vision returned to what she considered normal. On getting out of bed she experienced considerable difficulty in walking because she "could not tell the position in which she placed her feet and had to watch the ground constantly." The patient states, and her friends confirm the statement, that the hemorrhage was so severe that coal shovels and buckets were used to scoop up the clots after her delivery, so there can be no question that the loss of blood was unusually large although no blood studies were made at the time. At

the time of her observation at the Episcopal Hospital, during November and December 1932, the patient showed a suggestion of nystagmus, incoördination in finger-to-nose test, marked pyramidal tract and posterior column symptoms, diminution of visual acuity with evidence of old optic atrophy, concentric contraction of visual fields, normal gastric analysis and blood picture. Colloidal gold showed a low first zone alteration.

Case 2. A. S. was reported clinically by Dr. W. L. McConnell [9] in January 1907, and is included through the courtesy of Dr. William G. Spiller from his service at the Philadelphia General Hospital. The patient was admitted Dec. 12, 1903. At the time of admission the first blood examination revealed a hemoglobin of 16 per cent and 1,750,000 red blood cells. A few days before admission the patient, while in the county prison, had had a massive gastric or pulmonary hemorrhage. He had been in poor health previously. The following day he noticed dimness of vision. His sight gradually failed until one week after the hemorrhage vision was lost in both eyes. Shortly after the hemorrhage he experienced weakness in both legs and eventually entirely lost his ability to walk. Power in his legs, however, was never entirely lost. Three months after the weakness in his legs he began to experience weakness in both upper extremities. Improvement was very gradual and approximately 10 months later he was able to stand and walk a bit, although extremely ataxic. The following is a summary of notes made by Dr. Spiller on Aug. 4, 1904: "No facial weakness or nystagmus. The upper limbs are wasted. It is difficult to say whether there is any greater wasting in one part than the other. The biceps tendon reflex is present on each side though not very pronounced. Sensation in the upper extremities is normal. There is ataxia in the finger-to-nose test. Talipes-equino varus on each side. Voluntary power in lower limbs fair at knees, but almost lost at ankles; very feeble in all parts of lower limbs. Lower limbs extremely wasted in all parts. Abnormal position of feet readily overcome passively. Patellar reflex feeble on the left side and detected by a slight contracture of the muscles. The right patella reflex is completely lost. No Achilles; Babinsky distinctly present on each side. The patient is unable to stand. Sensory examination negative."

The following table shows the gradual recovery from the severe anemia on admission.

TABLE I

Date	Hemoglobin	Red Blood Cells	White Blood Cells
	Percentage		
12/23/03	24	2,100,000	4,600
1/4/04	35	2,450,000	5,800
1/13/04	44	2,720,000	4,400
1/27/04	48	2,700,000	4,000
2/27/04	41	2,370,000	4,300
3/5/04	44	3,000,000	5,400
4/12/04	62	3,350,000	5,500
5/18/04	85	4,630,000	5,600
8/30/04	76	5,760,000	8,000

It will be noted it was about six months before his blood reached approximately a normal level. His condition remained grave for some time, but gradually he improved. Loss of vision was permanent. For many years signs of pyramidal tract involvement persisted but eventually he was able to walk without any great difficulty. The last neurological examination of merit was by Dr. Fassey on October 14, 1921, and his findings are chiefly negative: Patient was blind; he presented no definite disturbance of gait or station; no sensory disturbance; tendon reflexes were all active and equal, with normal plantar reflexes. Free HCl was diminished and on one examination absent.

In 1924 the patient had a "stroke" and died a few days following it.

Pathologically the brain presented multiple areas of softening with advanced arteriosclerosis. The cord was flat and granular. These diagnoses were confirmed microscopically, and in the cord mild bilateral pyramidal tract degeneration was noted. Degeneration of the optic nerves was advanced. General autopsy showed moderate arteriosclerosis and broncho-pneumonia.

It is unfortunate that the cerebral softening complicated this case as the pathological findings are lessened in importance thereby, but there is little doubt of the gravity of the symptoms which date their onset from his severe posthemorrhagic anemia.

Case 3. E. B., female, aged 39, admitted to the service of Dr. Girvin, Presbyterian Hospital, March 14, 1932; discharged June 5, 1932. The patient had been having prolonged menstrual periods with profuse bleeding over a period of two years, each period lasting from three to 14 days and always being excessive. Fifteen days prior to her admission she had profuse bleeding with actual gushing at times. She was confined to bed four days prior to admission because of weakness and passed large vaginal clots. At the time of her admission she was extremely weak. The skin and mucous membranes were definitely blanched. Her blood pressure was 100 mm. of mercury systolic and 44 mm. of mercury diastolic. Vaginal examination revealed a soft cervix four fingers dilated through which a soft round mass was being expelled. A tentative diagnosis of incomplete abortion was made. Her temperature was 99.2; pulse 132 per minute; pupils equal, moderately dilated and reacted to light. The heart was enlarged slightly to the left; sounds distant; rhythm regular; and a systolic murmur was heard at the apex. Her hemoglobin on admission was 45 per cent; red blood cells 1,880,000; leukocytes 22,000.

The patient began to bleed profusely at midnight of the day of admission. The following morning she was given 300 c.c. of citrated blood and 2,500 c.c. of saline. On March 15 an attempt was made to evacuate the uterus under nitrous oxide anesthesia, but the bleeding was so profuse that the attempt was stopped. In the next few days the patient became extremely drowsy, confused, and was aroused only with some difficulty, and four days after admission became definitely blind and had little more than light perception. She was transfused as follows: March 15, 300 c.c. blood; March 22, 500 c.c.; March 25, 375 c.c. On March 19, when I first saw the patient, she was confused, blind and had a definite increase of muscular rigidity resembling a mild Parkinsonism, with some twitching movements, especially in the lower extremities. Her reflexes were all extremely hyperactive, but no Babinski was noted. Mental state was such that sensory examination was impossible. Again, on the twenty-first the patient was able to see objects moving in front of her eyes, but not distinctly. At this examination, with Dr. Cadwalader, there appeared to be evidence of very definite contraction of her visual field. The pupils reacted very slowly to light. There was no paralysis noted. Her reflexes were active and there was a suggestion of ankle clonus on both sides. The twitching movements previously noted were largely confined to the lower extremities and were irregular in nature. Gnostic sensations in the lower extremities were impaired. April 3 a note was made that there was a suggestion of paralysis of the upward associated ocular movements. Her expression was fixed. There was considerable rigidity with a suggestion of catatonia. Her general appearance suggested a developing Parkinsonian state. Her vision improved slowly but steadily, and by April 4, one month after admission, Dr. Langdon [10] stated that central vision tested with a card was about one-third of normal. On May 6 the patient's general condition having improved remarkably, hysterectomy and appendectomy were performed by Dr. Laws, and the patient was found to have an adenomyoma of the cervix of the uterus. At the time of her discharge from the hospital the patient's vision was normal in the left eye, with 6/12 vision in the right eye. Nerve heads were very pale and the visual fields were concentrically contracted.

This case is most interesting because of the fact that recovery from severe symptoms was apparently almost complete. Her hemoglobin three days after admission to the hospital had dropped to 27 per cent, with 1,200,000 red blood cells. After that, as a result of transfusions of some 2,000 c.c., the patient improved rapidly and these severe symptoms disappeared. The symptoms at the time of admission are remarkably like those of the first two cases. Only the prompt restoration of her blood by transfusion enabled this patient to survive and be restored. At the present time Dr. Langdon reports that her corrected vision is normal, but the visual fields are contracted. No recent neurological examination has been made.

In all three of these cases disturbance of vision was profound early in the course of their illness. Reports of transient and permanent blindness are not uncommon following hemorrhage. Hayes [11] in Norris and Oliver's "System of Diseases of the Eye" reports 11 cases following hemorrhage; 10 after gastric hemorrhage and one after hemorrhoidal bleeding. It is interesting to note that in all of these cases the hemorrhage was from a medical cause. Larrey,[12] in his medical memoirs of Napoleonic campaigns, in his discussion of diseases of the eye does not mention a single case of this sort, and the post World War literature does not reveal similar cases although massive hemorrhage was very common. Soldiers are usually in excellent health, and recovery from surgical hemorrhage is usually prompt.

It is interesting to theorize on the basis of the disturbances of the nervous system following a severe hemorrhage. The circulation apparently is kept adequate in the vital structures. The peripheral capillary bed is constricted with the resulting cold, pale skin and the common paresthesias. McGuigan and Atkinson [13] have shown that hemorrhage remarkably increases the response of the peripheral sympathetics to adrenalin. It appears that as long as this vasomotor constrictor action continues the blood is kept in vital parts, but should there be vasomotor relaxation the blood then enters the less vital parts, and changes may occur in the nervous system.

During anemia the resulting anoxemia, as shown by the work of Landis,[14] favors the development of edema with resulting impairment of function. Should this edema continue over a sufficient period of time permanent damage is sure to result, as in cases 1 and 2. Hemorrhagic anemia develops quickly, and there is little time for adjustment, so that anoxemia rapidly occurs with almost immediate disturbance of function of many portions of the nervous system. In all three cases there was profound disturbance of vision, locomotion and gnostic sensation very shortly after the massive hemorrhage. In cases 1 and 2 some of the symptoms were permanent and severe, while in case 3, where the oxygen carrying power of the blood was quickly restored by transfusion, recovery to almost normal health rather quickly occurred. The suggestive Parkinsonism and visual disturbance improved more slowly than other symptoms, possibly because the cells involved are more susceptible to anoxemia.

In secondary anemias from the slow loss or destruction of blood, symptoms of disturbance of nerve function are seldom a prominent feature, but are fairly constant. Visual disturbances, numbness, tingling and feelings

of coldness, generalized weakness, syncope, and rapid fatigue, resembling myasthenia gravis, are at times noted. In these cases blood is kept in the vital structures because the vasomotor control slowly adjusts itself. Unless the anemia is relieved, a sudden decompensation of the vasomotor system may occur and the vital centers be deprived of blood with resultant death. The brain and spinal cord in these cases show little more than intracellular changes because death occurs before more extensive damage can take place. In cachectic cases a comparatively small hemorrhage may be fatal because the already taxed vasomotor control suddenly decompensates.

Conclusions

1. Secondary anemia, especially posthemorrhage anemia, may produce organic alteration in the nervous system, the optic nerves and pyramidal tracts being most commonly involved. Disturbance of gnostic sensation may occur from anoxemia of nerve endings and not be permanent.

2. Prompt restoration of oxygen carrying power of the blood is necessary to prevent the described symptoms from being permanent.

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CASE REPORTS

ADENOMA OF THE PARATHYROID GLAND, WITH HYPERPARATHYROIDISM *

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During the past ten years great advances have been made in knowledge of the function of the parathyroid glands. Hypoparathyroidism, with the associated disturbance of calcium metabolism, is an important cause of tetany. Oversecretion of the hormone of the parathyroid glands (hyperparathyroidism) causes decalcification of bone, hypercalcemia, hypophosphatemia and increased calcium and phosphorus excretion in the urine. This condition results in the development of generalized *osteitis fibrosa cystica.* In most instances of hyperparathyroidism the changes in the skeletal system are the principal features, but occasionally, as in the case to be reported, renal symptoms predominate, and failure to recognize this fact may lead to error.

Case Report

Mrs. E. R., a 51 year old white female, was admitted to Vanderbilt University Hospital on April 29, 1935, complaining of pain in the left flank. The pain radiated around the abdomen, down to the genitalia and was associated with burning on urination. Seventeen years ago she had intermittent attacks of bilateral renal colic which lasted for nine months, associated with the passage of several small, dark brown stones. There were no more attacks until January 1935. During the first illness she was advised to discontinue eating meat, and, while on a low protein diet, developed sore tongue, roughness of the skin and swelling of the ankles. Because of these symptoms and pain in the back and lower extremities, she came to one of us on May 3, 1933. Roentgenograms of kidneys, left knee joint and left femur showed only thinning of the bones. The diagnoses of Paget's disease and nutritional edema were made and she was placed on a diet high in protein. On October 6, 1934, she returned because of swelling of the ankles, fatigue, nausea, vomiting, frequency of urination and nocturia. The urine contained some albumin and many pus cells. A serum calcium determination at this time was 13 milligrams per 100 c.c.† Because of the hypercalcemia and the roentgen-ray findings of decalcification of the long bones, the patient was placed on a high calcium, high vitamin, high protein diet. Three months later she developed an attack of renal colic, and from January to April 1935 had three such attacks. The patient grew progressively weaker, her appetite became poor, and she lost 15 pounds in weight. In addition, she had cardiac palpitation brought on by nervousness and exertion.

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† Normal serum calcium is 9 to 11 milligrams per 100 c.c. blood.

Past History. She had had scarlet fever at five years of age, influenza in 1918, and two or three attacks of sore throat. Her tonsils and appendix were removed 17 years ago. Her husband, one brother and one sister all have tuberculosis. She has had no symptoms of tuberculosis and repeated roentgenograms of the chest have been negative.

Physical Examination. Physical examination revealed a rather flabby, malnourished, apathetic individual, normally developed. She was very intelligent. The head was peculiarly pointed in shape, the cheeks had a hollow, sunken appearance, and the chin protruded forward. The pupils reacted normally to light and accommodation; the fundus examination showed some variation in the retinal arteries, but there were no hemorrhages or exudate. There was fullness over the thyroid gland but no masses were palpable. The heart and lungs were normal. The blood pressure was 120/74 mm. of Hg. Examination of the abdomen revealed distinct tenderness in the left flank. There was definite kyphosis of the dorsal spine and tenderness over the bones of both lower extremities. Pitting edema of the feet and ankles was present extending half-way up the legs.

Laboratory Data. Urinalysis: Specific gravity varied from 1.005 to 1.012; no albumin; sediment contained five to six red blood cells and an occasional white blood cell; the benzidine test was positive. Blood: The red blood cell count was 3,760,000; hemoglobin 13 grams; white blood cell count 13,000. The blood smear was normal. Wassermann and Kahn tests were negative. The basal metabolic rate was minus 9 per cent. The phenosulphophthalein renal function test (intravenous) was 55 per cent. The blood non-protein nitrogen varied between 25 and 41 milligrams per 100 c.c. The serum phosphatase was 7 units per 100 c.c.* The serum protein was 6.8 per cent, with 4.3 per cent albumin and 2.5 per cent globulin. The serum calcium was 12.9 to 13.5 milligrams per 100 c.c. The serum inorganic phosphorus was 2.1 to 3 milligrams per 100 c.c. Roentgen-ray examination revealed a large ureteral calculus in the upper segment of the left ureter. "The wing of the left ilium showed marked thickening with striations and also a large area of osteitis in the left sacro-iliac region. There was considerable hypertrophic arthritis of the lumbar spine. There was marked thickening of the bones of the skull. The bones of the hand showed marked thinning of the cortex." (Dr. C. C. McClure.) Because of the apparent disturbance in calcium metabolism, it was decided to investigate this more fully. The calcium metabolism was studied as follows: The patient was put on a low calcium diet containing 0.3 grams of calcium per day. After five days on this diet the whole of the urine and feces were collected for a three day period, the former as separate 24 hour specimens, and the calcium content of these was determined. Before commencement of the test period, and at the conclusion of the period, the patient received cachets of carmine, the appearance of the dye in the feces serving as an indicator for the demarcation of the period of observation. The total output of calcium for the three day period was 1,335 milligrams, of which 931 milligrams appeared in the urine and 424 appeared in the feces. In other words, 70 per cent of the total amount of calcium excreted appeared in the urine.† This study was repeated twice with similar results.

Diagnosis. The skeletal decalcification, polyuria, nycturia, hypercalcemia, hypophosphatemia and calcium metabolism studies indicated the presence of hyperparathyroidism. An exploratory operation was done on May 29, 1935, with the expectation of finding an adenoma of a parathyroid gland or parathyroid hyperplasia. Dr. Barney Brooks found a parathyroid tumor 2.5 cm. in length and 1 cm. in diameter in the region of the left lower lobe of the thyroid. (Figure 1.)

Pathological Report. The specimen was a very soft, dark purple, club-shaped, smooth encapsulated tumor. A thin capsule was opened and a layer of blood was

* Normal serum phosphatase is 6 to 12 units per 100 c.c. blood.

† In a normal individual on a similar diet, only 10 to 30 per cent of the total calcium excreted appears in the urine, the remaining 70 to 90 per cent being present in the feces.

released. This revealed a brownish-yellow, dull, smooth tumor mass about one-half the size of the specimen. On cut section it had a smooth, homogeneous appearance and was light caramel in color. Dr. Goodpasture's report on the section was as follows: "The microscopic section consists of a very cellular, irregularly elliptical

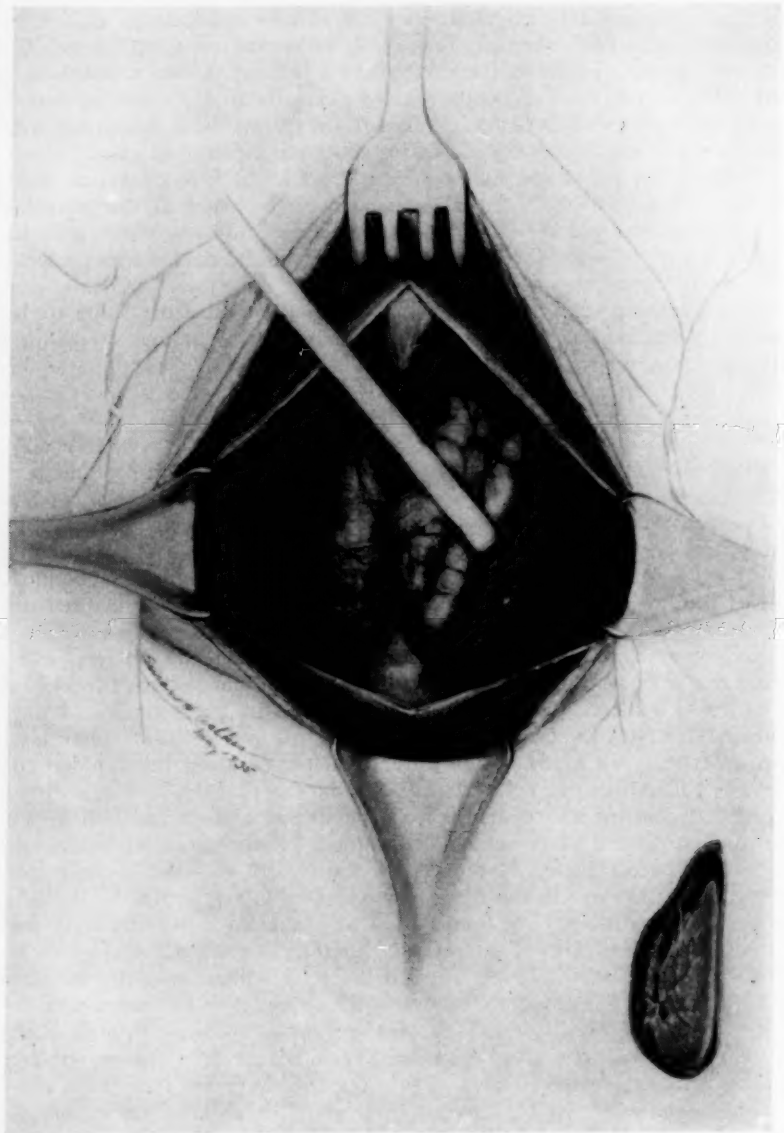

FIG. 1. Adenoma of the parathyroid gland.

piece of tissue measuring 12 by 5 millimeters. Nuclear material as compared with cytoplasm is very abundant so that the tissue stains deeply blue with hematoxylin-eosin. Under low power the tissue seems to be quite uniform in appearance, consisting of epithelial cells arranged in small acini and alveoli compactly situated with very

little stroma and a rich collapsed capillary bed separating them. There are several medium-sized arteries and veins tracing through the substance of the tissue. The composition of the tissue is not entirely uniform because there are several areas situated toward the center of the mass which are less cellular than the surrounding tissue and in which the alveoli are thinned out and often arranged in strands. Here the nests of epithelial cells are widely separated by spaces containing a pink granular precipitate. These spaces appear to be greatly distended lymphatics. In other foci the epithelial cells are compact but contain a relatively abundant pink-staining granular cytoplasm, so that these areas have a paler pinkish appearance in contrast to the denser surrounding areas. Where the alveoli have an acinar arrangement the epithelial cells are low cuboidal in shape, and their nuclei are situated toward the basement membrane. Throughout the section the cytoplasm of the cells is faintly pink, containing amorphous granular material and sometimes the cytoplasm appears to be washed out, but in general the epithelial cells throughout the section have irregular basophilic condensations within the cytoplasm. There are a few areas of adipose tissue infiltration within the glandular substance. While for the most part the cells are fairly uniform in size and have regular oval nuclei, there are a great many hypertrophic nuclei scattered irregularly throughout, and there are small foci in which the cytoplasm is greatly increased in amount without change in size of the nuclei. In such cells the cytoplasm has a uniform, fine pink granulation and no mitotic figures were seen. There is a distinct but thin capsule surrounding about half of the section and into this there is an irregular growth of glandular acini. There is, however, no evidence of malignancy. The tissue is typically that of the parathyroid gland, and the condition is one of hyperplasia of the glandular cells. Because of the localized character of the parathyroid enlargement, involving only one gland, the nature of the new growth may be regarded as neoplastic; that is, adenomatous in the sense of Castleman and Mallory.[1]

Subsequent Course. The patient stood the operation well and the first postoperative day was uneventful (May 30, 1935). On the morning of May 31, the second postoperative day, she developed a sensation of oppression in the chest, increased irritability, tingling in the fingers, and positive Chvostek and Trousseau signs. The serum calcium was 9.1 and phosphorus 2.2 milligrams per 100 c.c. For 10 days she had symptoms of tetany, which were easily controlled by the administration of 8 c.c. of 40 per cent calcium chloride four times a day and two doses of calcium gluconate intravenously on the third and fourth postoperative days. At no time was it found necessary to give Collip's parathyroid extract. By June 28, 1935, it seemed probable that she could not pass the stone in the left ureter and on that day it was removed by Dr. E. H. Barksdale.

The partial analysis of the stone was as follows: Weight of stone (oven-dry): 155.6 milligrams; $Ca_3(PO_4)_2$ 38.1 per cent; CaC_2O_4 (oxalate) 43.4 per cent; urates, trace; carbonate, trace; cystine, trace; percentage of stone as Ca, 28.3 per cent.

The patient's recovery was uneventful and she was able to leave the hospital on July 13, 1935; her only symptom was occasional mild tingling in the arms.

Re-admission. The patient was readmitted to the hospital on September 9, 1935, for calcium metabolism studies. Her only complaints were edema of the ankles and symptoms suggestive of mild tetany. She had gained 23 pounds in weight and felt better than ever before. The physical examination revealed a cheerful, adult female. The skin was warm, dry, and there was a papular pruritic rash with an erythematous base over the ankles and the lower part of each leg. The spine and extremities were not tender. The neurological examination was negative.

At this time the laboratory data were as follows: Urine: Specific gravity, 1.007, no albumin, sediment: three to four white blood cells, no red blood cells. Blood: Red blood cell count 4,000,000, white blood count 8,000, hemoglobin 12.2 gm. Venous

pressure in the arms was 85 millimeters of saline. Blood non-protein nitrogen 38 milligrams per 100 c.c. Serum protein 6.4 per cent, albumin 4.4 per cent and globulin 2.0 per cent. Serum calcium 9.8 milligrams per 100 c.c. Roentgen-rays showed little change in the cranial bones, but the wing of the left ilium showed bone structure much nearer normal than on any previous occasion.

The metabolic studies were repeated and are shown together with the preoperative studies in table 1. Compared with the preoperative period when the total calcium excretion for three days was 1,335 milligrams, of which 931 milligrams appeared in the urine and 424 milligrams in the feces, the total excretion now for three days was only 558 milligrams, of which 169 milligrams appeared in the urine, and 389 milligrams in the feces.

TABLE I

Calcium Excretion on Low Calcium Diet before and after Removal of Parathyroid Adenoma (three-day metabolism period; diet containing approximately 0.3 gm. calcium per day)

5/15/35–5/17/35 (Before) Gm. Calcium		9/15/35–9/17/35 (After) Gm. Calcium	
Urine	Feces	Urine	Feces
0.931	0.425	0.169	0.389
Per cent excreted in urine..69%.....			30%

The values of the preoperative and postoperative serum calcium and phosphorus determinations are represented in figure 2. Before operation, the serum calcium was high, ranging from 12.5 to 13.5 milligrams per 100 c.c. and the serum inorganic phosphorus was low, varying from 1.7 to 3 milligrams per 100 c.c. After recovery from the operation the serum calcium varied from 9.8 to 10.1 and the serum inorganic phosphorus from 3.0 to 4.7 milligrams. These findings indicate clearly that the hormone from the adenoma was directly concerned in the hypercalcemia which was present before the operation.

DISCUSSION

Von Recklinghausen [2] in 1891 first called attention to the condition known as *osteitis fibrosa cystica*. He emphasized the generalized nature of the disease pointing out that it affected all the bones, thus differing from the solitary cysts of bone or benign giant cell tumors. In 1904, Askanazy [3] first described a case of *osteitis fibrosa cystica* associated with a parathyroid adenoma. Erdheim [4] in 1907 described three cases of osteomalacia associated with parathyroid tumors. In 1923 Dawson and Struthers [5] pointed out the frequent association of renal calculi with the presence of areas of metastatic calcification in the lungs, kidneys, and myocardium in cases of *osteitis fibrosa cystica*. It was not until 1926, however, that Mandl [6] performed the first operation for the removal of a parathyroid tumor in a case of *osteitis fibrosa cystica*. The patient completely recovered.

Collip [7] in 1925 discovered parathormone and studied the effect of experimental hyperparathyroidism. He found that the essential characteristic was the development of hypercalcemia sometimes exceeding 20 milligrams per 100 c.c. of serum.

In 1930 Hannon, Shorr, McClellan and DuBois [8] studied the biochemical aspects of *osteitis fibrosa cystica* and through their investigations definitely established the presence of hypercalcemia and hypophosphatemia. In the same year Bauer, Albright and Aub [9] described the increased urinary output of cal-

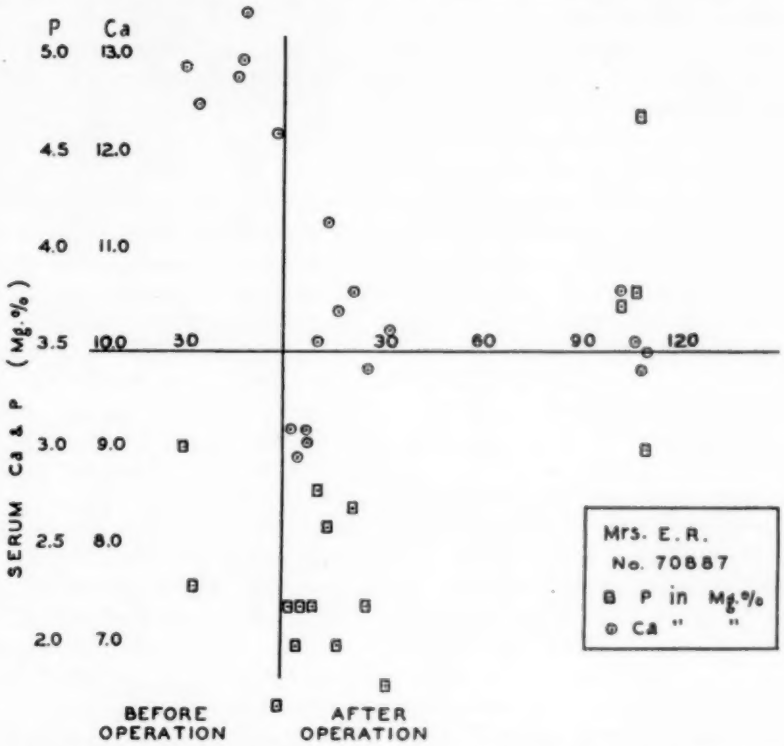

FIG. 2. Calcium and phosphorus studies made before and after operation. The numbers on the longitudinal ("normal") line indicate days before or after operation. The day of operation is indicated by the vertical line.

cium and phosphorus in a case of *osteitis fibrosa cystica*. They found it to be six to seven times greater than in the normal individual. They also found that these changes in metabolism were equivalent to those of a normal individual receiving 100 units of parathyroid hormone daily. Excellent reviews of the subject of hyperparathyroidism have been published, notably by Hunter and Turnbull,[10] Barr and Bulger [11] and Jaffé.[12] Recently Castleman and Mallory [1] have studied the histology of the parathyroid glands in cases of hyperparathyroidism.

In 1934 Albright, Aub and Bauer [13] reported 17 proved cases of hyperparathyroidism. They gave a detailed description of the condition and described the following clinical types: (1) classic hyperparathyroidism (Von Recklinghausen's disease). Skeletal manifestations predominate and consist of decalcification, cysts, tumors and eventually fractures. (2) Osteoporotic form of hyperparathyroidism. Presenting symptoms are due to general decalcification and there are no cysts or tumors. (3) Hyperparathyroidism with

nephrolithiasis. Presenting symptoms are associated with renal stones and with no gross skeletal changes. (4) Hyperparathyroidism with renal insufficiency (nephrocalcinism). The symptoms are those of Bright's disease. (5) Acute parathyroid poisoning. This is a condition simulating acute parathyroid poisoning in dogs with sudden death and characteristic pathologic changes. (6) Hyperparathyroidism simulating (or complicated by) Paget's disease. In this classification our patient belongs to types 2 and 3, presenting renal symptoms extending over a period of 17 years, and finally, manifestations of generalized decalcification without cysts or tumors.

Comments

In view of the increase in the number of reported cases in recent years, a resumé of the important clinical features of hyperparathyroidism is given. This disease may occur at any age period. The youngest patient reported by Bauer, Albright and Aub was 13 years of age and the oldest 62 years of age, although most cases fall in the middle age group. The sexes are equally affected.

Although a positive diagnosis cannot be made without chemical data, the symptoms of hyperparathyroidism are usually quite characteristic. The onset is insidious and may consist only of mild pains in the bones. In the instances where the skeletal changes predominate, a spontaneous fracture may be the first event that calls attention to the disease. In more advanced hyperparathyroidism muscular weakness, lassitude and hypotonia are constant symptoms and may finally lead to difficulty in coördination. There is diminished irritability of muscle to electrical stimulation. These symptoms are attributed to the hypercalcemia. Many patients with the disease are classified and treated as neurasthenics prior to the recognition of the true nature of their symptoms.

Hyperparathyroidism with renal manifestations may present symptoms exclusively renal and these may have persisted for many years. These are symptoms of renal calculus, pyelitis, pyelonephritis with or without gravel. Increased thirst, which is attributed to the increased excretion of calcium and phosphorus, is commonly present. Polyuria, however, is not always present and it is interesting to note that when it occurs the incidence of stones is less. Bone symptoms may be vague or entirely absent. Albright, Baird, Cope and Bloomberg [14] in a study of the renal complications of hyperparathyroidism emphasize that all of the symptoms and signs of nephritis may be present. They stress the importance of the recognition of the accompanying bone changes in the diagnosis of the underlying hyperparathyroid state in such cases. They further point out that with profound kidney damage there is interference with calcium and phosphorus excretion in the urine. Albright, Aub and Bauer [13] report eight instances of hyperparathyroidism discovered as a result of performing routine blood calcium and phosphorus determinations in all patients with urinary calculi.

Clinically, hyperparathyroidism may resemble other conditions as osteomalacia, solitary cysts, Paget's disease, senile osteoporosis, solitary benign giant cell tumor, osteogenesis imperfecta, multiple myeloma, metastatic malignancy, renal rickets and basophilic adenoma of the pituitary (Cushing's disease). An excellent discussion of the differential diagnosis is given by Albright, Aub and Bauer,[13] by Jaffé,[12] and by Gutman, Swenson and Parsons.[15]

Hyperparathyroidism cannot be accurately diagnosed without the demonstration of the presence of biochemical disturbances which occur in the body as a result of the over-secretion of the parathyroid hormone. Of significance are high serum calcium and low serum phosphorus values in the blood. These values may vary from 12.5 milligrams to over 20 milligrams of calcium per 100 c.c. of serum, and from 1.0 to 3.0 milligrams per 100 c.c. of inorganic phosphorus. These metabolic changes are not in themselves diagnostic, for high calcium values may occasionally be observed in multiple myeloma, metastatic carcinoma of bone, and in certain diseases accompanied by hyperproteinemia. Moreover, in not a few instances of hyperparathyroidism the inorganic phosphorus may be normal. The most convincing chemical evidence of hyperparathyroidism is the demonstration of alterations in the calcium balance controlled over a period of time on a fixed low calcium diet. A negative balance indicating an excretion of calcium in excess of that ingested strongly supports the diagnosis. Although calcium excretion in the feces varies with the intake, the urinary calcium nearly always maintains an abnormally high level in hyperparathyroidism. In certain instances, however, as in severe nephritis associated with renal insufficiency, the urinary excretion of calcium may be diminished and confuse the picture. In these cases the roentgen-ray evidence of generalized decalcification of bone will constitute a significant diagnostic finding.

Roentgen-ray findings, when they do exist, consist chiefly of deformities, cysts, tumors, fractures and evidence of generalized thinning of bone. This is best seen in the flat bones and in the skull. Occasionally irregular thickening may be observed in the temporal, parietal and frontal bones of the skull, but more commonly there is definite evidence of decalcification. In instances of renal involvement without bony changes, metastatic calcified areas in the kidneys may be present. The most important roentgen-ray finding, however, is a progressive thinning of all bones.

Treatment. The medical treatment of hyperparathyroidism is of no value. Diets high in calcium and phosphorus may prevent the decalcification of bone, but increase the incidence of renal calculi. It is generally agreed that vitamin D is of little value. The treatment is surgical and the surgeon may expect a good-sized tumor in cases with marked hyperparathyroidism. But he must be a good surgeon and courageous for one does not always find the tumor at the common site for the parathyroid glands. A search for the tumor may lead him into the anterior mediastinum. It must be borne in mind that removal of a normal parathyroid gland is dangerous and may lead to marked postoperative tetany which may be fatal. The surgeon must also exercise careful judgment in deciding upon how much to remove. For here, as in the thyroid, the decision between a sub-total removal and complete extirpation may affect the future of the patient's life. It must also be borne in mind that parathyroid tumors may be multiple and if the removal of one does not cure the patient, a second operation may have to be performed at a later date.

The complication that arises after operation is postoperative tetany. Increased irritability of the muscles, carpo-pedal spasm, positive Chvostek and Trousseau signs may appear within the first 24 hours after the operation. They are accompanied by marked diminution of calcium in the urine, and return of the serum calcium to normal or subnormal values. The low values may persist

for weeks and even months after the operation. The control of postoperative tetany is obtained by the administration of calcium by mouth, calcium gluconate intravenously and Collip's parathyroid extract. Calcium in some form must be administered frequently, as it is very rapidly excreted. Eventually a readjustment of the activity of the remaining parathyroid tissue occurs and these symptoms disappear.

The improvement following operation is dramatic. The patient's general appearance changes; lassitude is replaced by a feeling of energy and the bone pains immediately disappear. Changes in bone structure may be observed by repeated roentgenographic examinations. Although these changes do not parallel the marked symptomatic improvement the bones eventually present a normal appearance.

Summary

A case record of adenoma of the parathyroid gland, with hyperparathyroidism and renal calculus (calcium stone) is presented. The preoperative diagnosis was based on a history of renal colic for many years, the roentgenographic evidence of decalcification of bone, and the presence of a negative calcium balance with hypercalcemia, hypercalcinuria and hypophosphatemia. An adenoma of the parathyroid gland was removed at operation. Prompt recovery from the hyperparathyroid state ensued.

Calcium metabolism studies made before and after operation are recorded.

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SUBACUTE BACTERIAL ENDOCARDITIS OF THE MITRAL VALVE PREVIOUSLY RENDERED INCOMPETENT BY INFARCTION OF THE PAPILLARY MUSCLE AND SHORTENING OF THE CHORDAE TENDINAE*

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THE present communication is made as a contribution to the study of two problems: first, the production of murmurs in coronary infarction; and second, the pathogenesis of subacute bacterial endocarditis. The occurrence of murmurs and of subacute bacterial endocarditis in relation to coronary infarction have both been repeatedly reported. The significance which I wish to attribute to them in the light of the case to be reported is new.

CASE REPORT

Male, aged 53 (at the time of the attack), suffered a coronary infarction on January 2, 1931. The evidence was convincing. He had pain in his chest and numbness of his arms. The pain in his chest was over the sternum and precordium. The patient did not remain quiet, but was constantly moving about. The pain came on during the night and lasted several hours when he summoned me about 6 a.m., January 2. At that time the blood pressure was 180/120 mm. of Hg; the heart rate was 80, without any abnormalities of rhythm or sound; A_2 was accentuated. On January 3, the temperature rose to 101°, the pulse to 100, and the respiration to 30. The blood pressure was 175 systolic and 100 diastolic. On January 4, the temperature rose to 101°, the pulse was 100, respiration 20, and the blood pressure was 160/115 mm. of Hg. On January 5, the temperature was 100.5°, the pulse 80, and the blood pressure was 135/100. On January 6, the blood pressure was 125/90, and there was a soft systolic murmur at the apex. On January 7, sternal pain recurred during the night; temperature 100.5°, blood pressure 120/90. By January 9, the murmur had changed from the soft character previously described to the "zwing" of the jew's-harp character. The temperature continued to rise to 99 to 99.4°. On January 10, the blood pressure was 90/65 mm. of Hg, on January 11 it was 106/75, on January 12, 116/85, and on January 14, 130/95. There was then a systolic murmur at the second left interspace, but it was not musical there as it was at the apex. On January 16, the blood pressure was 116/90 and the heart rate 76, and on January 20, the blood pressure was 130/100. The electrocardiogram made on January 20 showed: Auricular rate 80, ventricular rate 80, sinus rhythm. P–R interval, 0.16 sec., Q.R.S.,

* Read by title at the Meeting of the Association of American Physicians, May 1935.
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0.09 sec. Left axis deviation. T_{2-3} inverted. In the second lead the T take-off was high and the S–T interval above the iso-electric line. Slurring of Q.R.S. in all three leads.

In April 1931, he had a slight elevation of temperature again to 101.5°, and with this some bloody sputum. There were, however, no abnormalities found in the lungs on physical examination. A roentgen-ray report on May 16, 1931 was as follows: "Examination of Chest: The right diaphragm is well within normal limits. The left diaphragm is resting at a level somewhat higher than the right, which reverses the

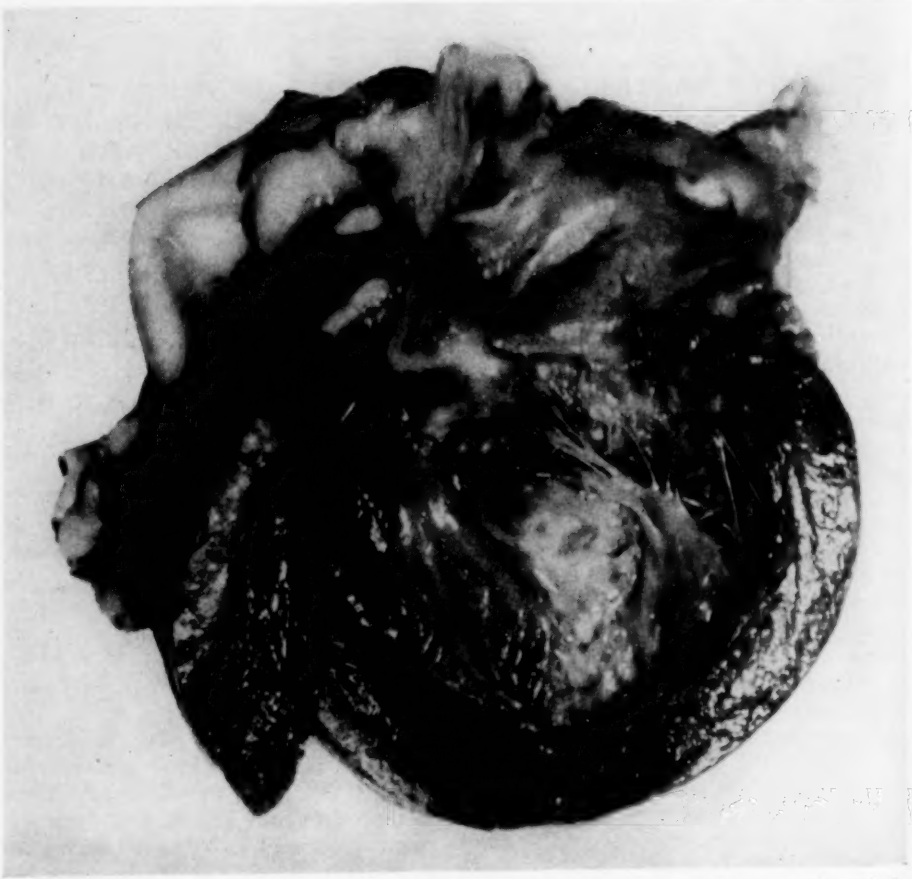

FIG. 1. Infarct of the intraventricular septum involving the papillary muscles of the posterior flap of the mitral valve. Subacute bacterial endocarditis attacking the mitral valve.

usual position. However, the left diaphragm appears to be elevated by a large amount of gas contained in the stomach and colon beneath the diaphragm, probably elevating this. The heart shadow measures 5 cm. to the right, 11½ cm. to the left, or a total of 16½ cm., while half the inside diameter of the chest measures 15½ cm. The heart is therefore considered to be 1 cm. larger than the standard for comparison. The aorta is within normal limits. The pulmonary fields show no visible evidence of pathologic change."

In November 1931, he again had some bloody sputum, but throughout 1931, until

the summer of 1932, he felt remarkably well and was quite active, even playing golf without fatigue. In August 1932, he had another febrile attack, with temperature rising to nearly 103°. He was sick nearly two weeks, during which time he again spat blood. The blood pressure had continued to range from 135 to 155 systolic, and from 100 to 110 diastolic. He had been made to lose considerable weight, 25 to 30 pounds, by restriction of intake of food, so that by June 1933 he weighed 143 to 145 stripped, less than he had weighed for 20 years. He had continued to play nine holes of golf without dyspnea or fatigue. This had been permitted in spite of great concern on my part. In December 1933, the blood pressure was 165/125. The electrocardiogram on January 9, 1933 was as follows: Auricular rate 103, ventricular rate 103; P–R interval, 0.17 sec.; Q.R.S., 0.10 sec.; left axis deviation; slight shift down of S–T_1; slight slurring of R_1 and downward direction of R_2; low T_{1-2-3}; deep Q_3; P_3 diphasic. On June 9, 1934, the following note was made. "He has continued to play nine holes of golf three times a week. He is never out of breath, walks slowly and ascends stairs slowly. Has no longer any chest pains; only once in five months has he had these pains, and then at night. They passed off after he had eaten a few candies. He considers his heart better; it gives him much less concern. His nerves are in bad shape, in fact throughout the years he had been under very great nervous strain, and has had occasion for worrying a great deal. He has always slept restlessly and suffered much from insomnia, for which it was necessary for him to take amytal frequently."

Beginning on June 19, 1934, he was in bed for 18 days because of fever rising to 102° for which no cause could be found. After he was free of fever for 10 days he was allowed up again, but he never regained his strength, and during July he continued to complain of lassitude. On August 2, it was noted that he had temperature of 99.2°, and he was sent home again to bed. The temperature began to range then from normal in the morning to a maximum of 101° in the evening. No definite cause for the temperature was found until a blood culture, taken on August 11, showed *Streptococcus viridans*. The number of colonies increased rapidly, and on September 23, there were 250 colonies of *Streptococcus viridans* per cubic centimeter of blood. Repeated transfusions of whole blood, 250 c.c. each time, were given at intervals of a week from August 17 to October 18. Although the number of colonies diminished, so that on October 16 there were only two colonies per cubic centimeter of blood, the condition throughout September and October remained about the same except for a progressive loss of weight. There were never any petechiae. The second week in November he had great tenderness of the palms of both hands over the pads at the base of the phalanges, and also on the soles of the feet at the base of the phalanges. This tenderness lasted for a few days. Throughout September, October and November there was great soreness and stiffness of the neck muscles. The spleen was never felt, and there never was any indication of embolism in the spleen or elsewhere. The temperature range throughout September, October and November was low, usually to a maximum of 100.5°, occasionally to 101°. On November 12, the temperature rose to 103°, and the next 10 days to his death on November 21 were quite stormy. On November 12, he had a coughing spell, becoming very hysterical. The next night there was a sudden edema of the lungs, and the patient was practically pulseless. The surface of the body was cold and clammy. He was apparently moribund on November 14, 15 and 16, but on November 17, he was better and even oriented at times. The temperature ranged up to 103°. On November 18, 19 and 20, he was in delirium and stupor, practically pulseless. On November 20 and 21, there was dullness throughout the right lung posteriorly with bronchovesicular breathing, and dullness and crepitant râles at the base of the left lung. He died on November 21. Respirations had gone to 60, the temperature to as high as 105°.

I am indebted to Drs. John A. Lanford, Samuel Colvin and Kurt Neugarten for the following notes on the autopsy.

Autopsy Report. The body is that of a white male, apparently 50 years of age, approximately 5 feet 11 inches in length, and weighing about 150 pounds. The body shows some evidence of loss of weight, although the fat is still normally distributed. No petechiae are noted. The thorax is well developed and of the sthenic habitus. The abdomen is slightly distended. There are no scars. The left side of the scrotum reveals a left hydrocele measuring about 6 cm. in diameter, and containing approximately 50 c.c. of light straw colored fluid. The extremities show no changes. The cervical and axillary lymph nodes are not enlarged but the inguinal nodes show slight adenopathy.

Peritoneal Cavity. The peritoneum is smooth and glistening. There are about 500 c.c. of straw colored fluid present. The appendix is normal. The urinary bladder is not distended. The spleen is enlarged in size and in its usual location, as is the liver. The other abdominal viscera are in their normal positions. The diaphragm extends to the fifth rib on the right side and the fifth intercostal space on the left. The mesenteric lymph nodes are not enlarged. The stomach and intestines are greatly dilated.

Thoracic Cavity. The parietal pleurae are smooth and glistening. There is no free fluid present and only a few recent fibrinous adhesions on the outer side of the lower lobe of the right lung. The right lung shows a large solid area involving almost entirely the lower middle and part of the upper lobes. The left lung shows only patches of pneumonia here and there. The heart is in its usual location but is greatly enlarged.

Heart and Pericardium. The parietal pericardium is covered over nearly its whole extent with a light cheesy appearing material. About 20 c.c. of cloudy fluid containing many small flecks of fibrin are present. The fibrinous exudate is particularly abundant over the right auricle and the great vessels, less so over the left auricle and left ventricle. The heart is considerably larger than normal. It has lost the normal conical shape. There is a moderate amount of fat beneath the epicardium through which the muscle appears as brownish-red in color. Over the right ventricle and to a considerable extent over the posterior aspect of the left ventricle, this brownish-red muscle exhibits irregular areas varying in size shining through the epicardium as islands with a large grayish-yellow center and a pinkish-red periphery (areas of apparent necrosis). At the posterior sulcus longitudinalis there is a large dull ivory white area (3 by 5 cm.). This involves chiefly the left ventricle but extends also for a small distance to the right ventricle. Palpation reveals this area to be thinner and less resistant than the rest of the ventricular wall; yet one has the impression that it is more solid: a thin fibrous scar.

The right auricle, somewhat increased in size, is partly occupied by an *ante mortem* thrombus (fibrinous mass) which completely fills up the auricular appendage and extends into the upper half of the auricle. Beneath this exudate the endocardium is partly ulcerated. The tricuspid and pulmonary valves are normal. The tricuspid orifice admits four finger tips. The foramen ovale is closed. The chamber of the right ventricle is also increased in size. Sections through its wall show irregularly scattered areas of necrosis similar to those already described as seen on the external surface of the heart.

The chamber of the left auricle is markedly dilated. The mitral orifice admits two finger tips. Here the endocardium is thick, grayish-white, and the muscle is not to be seen through it. There is an ulceration (3 by 2.5 cm.) on the anterior left lateral wall of the chamber. This extends down on to the auricular surface of the mitral valve. On the endocardium above the line of attachment of the posterior mitral flap, there are flat, granular, grayish-pink vegetations with two tongue-like continuations upon the floating part of the valve. These "tongues" reach the free edges of the valve and present a picture resembling a horseshoe. Besides these vegetations on the

auricular aspect of the posterior flap, there are other similar ones toward the aortic flap of the mitral valve, chiefly where the two flaps are joined anteriorly. These vegetations vary from miliary to lentil size and consist of smooth grayish-white fibrinous verrucae upon which pinkish granular punctiform spots are seen here and there. These vegetations continue upon the ventricular aspect of the valve and also for almost 1 cm. upon the chordae tendinae of the posterior flap of the valve.

The left ventricular chamber is somewhat ballooned out, this being particularly noted in the posterior part of the interventricular septum corresponding to the region of the fibrous scar previously described. The internal aspect of this area is grayish-red and differs distinctly from the surrounding brownish-red of the rest of the ventricular wall. The endocardium, however, is smooth. The upper corner of the oval shaped area of the scar forms a deep depression in the muscular wall. There, the trabeculae carneae have completely disappeared leaving only small flattened bridges at the base of the scar. Further, one notes a difference in the structure of the anterior and posterior ventricular wall (internal aspect) as well as of the papillary muscles. The anterior papillary muscle and the trabeculae carneae of the anterior wall have their normal shape. The posterior papillary muscle, the base of which is included in the scar, is shortened and appears as a flat strip merging into the ventricular wall. The tips of the papillary muscle can no longer be seen. The thin smooth chordae tendinae are stretched. They hold the posterior flap of the mitral valve down against the posterior wall of the ventricle so that during life only slight movement of this posterior flap could have been possible.

The attached portion of the aorta shows some slight thickening in the sinuses of Valsalva around the orifices of the coronary vessels. The right coronary when opened is found completely thrombosed. The left coronary is thickened and its lumen generally narrowed, being represented by a mere pin-point opening. It is free from thrombus formation except in its smaller subdivisions. The aortic cusps are normally thin and smooth. The wall of the left ventricle measures 13 to 15 mm. in thickness and on section has a mottled appearance. There are dirty yellow areas surrounded by a brownish-red ring.

Lungs. The right lung measures 22 cm. in length, 12 cm. in width by 6 cm. in thickness. The external surface shows a massive area of bluish-black discoloration extending over the entire surface with the exception of a small area along the periphery of the lower lobe and the upper half of the upper lobe. Along these latter areas are small patches of emphysematous tissue. The remainder of the lung is solid and of the consistency of liver, and on section is deep red in color and upon pressure only bloody material escapes, there being no air in this portion. A bloody frothy fluid escapes from the periphery. Weight 750 grams.

The left lung measures 22 cm. in length, 11 cm. in width by 5 cm. in thickness. The external surface is pinkish-red in color and is streaked with areas of bluish-black scattered throughout both lobes. The cut surface is pinkish-red in color for the most part, and upon pressure exudes a frothy blood-tinged fluid. There are some small consolidated areas throughout the parenchyma, several of which are somewhat triangular in shape. Weight 425 grams.

Liver. The liver measures 20 cm. in length, 26 cm. in width by 7 cm. in thickness. Its external surface is smooth and glistening, and brownish-red in color, mottled with many small areas of yellowish discoloration. Upon section, the organ is typically nutmeg in appearance and generally congested. Innumerable small yellowish-white specks stand out prominently. The organ is very much enlarged. Weight 1615 grams.

Gall-Bladder. The gall-bladder is almost collapsed and contains only a small amount of bile. No stones are palpated. The external surface is adherent to the omentum and is torn away with much difficulty. It is pinkish-yellow in color, smooth and glistening except in the adherent areas.

Adrenals. The adrenals are pyramidal in shape, measuring 4 to 3 cm. The external surface is slightly lobulated and pinkish-yellow in color. Upon section, the cortex is dirty yellow in color and not well differentiated from the medullary portion.

Kidneys. The left kidney measures 12 cm. in length, 7 cm. in width by 5 cm. in thickness. There are several large retention cysts seen externally, extending into the kidney tissue for 1½ cm. in depth. The external surface is lobulated and granular in appearance. The capsule strips with some difficulty revealing a granular pinkish-red congested surface. The cut surface reveals a cortex which is well differentiated and measures from 5 to 7 mm. in thickness. The organ is congested in appearance. There is a large amount of fat in the pelvis. Weight 190 grams.

The right kidney measures 12 cm. in length, 6 cm. in width by 5 cm. in thickness. It varies in no way from the left kidney with the exception that the retention cysts found here are much smaller than in the left kidney. Weight 175 grams.

Pancreas. The pancreas measures 20 cm. in length, 4 cm. in width by 1½ cm. in thickness. Its external surface is pinkish-yellow in color and lobulated in appearance. The cut surface is yellow in color and lobulated. The organ shows no gross changes with the exception that it is more flabby than usual. Weight 110 grams.

Spleen. The spleen measures 15 cm. in length, 10 cm. in width by 5 cm. in thickness. Its external surface is grayish-red in color and smooth and glistening with the exception of two large raised infarcts which are present at the upper and lower poles respectively. These infarcts are pale pinkish-orange in color and are sharply demarcated from the surrounding tissue. Upon section they are 1½ cm. and 1 cm. in diameter respectively, both exuding a purulent yellow discharge from their bases. The infarcts themselves are necrotic and friable. The remainder of the cut surface of the spleen is deep red and congested in appearance, with innumerable small yellowish areas of focal necrosis seen scattered throughout the surface. Weight 300 grams.

Gastrointestinal Tract. The stomach is greatly distended with air, as are the entire small and large intestines, especially the cecum.

Blood culture, taken at autopsy under sterile precautions, shows the presence of *Streptococcus viridans.*

Anatomical Diagnoses: Coronary thrombosis with infarction (old and recent); *Streptococcus viridans* septicemia; subacute bacterial endocarditis, mitral; acute and chronic myocarditis; ante-mortem thrombus of right auricle; pericarditis, fibrinous; lobar and lobular pneumonia; chronic nephritis; multiple infected infarcts of spleen; passive congestion of liver and spleen; hydrocele.

The Significance of Murmurs Occurring in Coronary Thrombosis and Cardiac Infarction

Murmurs in cases of coronary thrombosis are mentioned by most writers. Paul White,[1] for example, writes: "Murmurs may or may not occur; the commonest is that of functional mitral regurgitation due to dilatation—an apical systolic murmur—although at times a sclerotic change involving the base of the mitral valve may result in organic mitral regurgitation. Basal murmurs are less common in coronary disease; an aortic systolic murmur may be found, due to aortic dilatation, in turn usually resulting from an associated hypertension, but sometimes such a murmur is due to aortic stenosis caused by sclerotic involvement of the aortic valve; if this latter process is marked a systolic thrill will be felt over the aortic area and will be transmitted into the neck. An aortic diastolic murmur is much less common but may result from either of the lesions just noted which produce the aortic systolic murmur." Samuel Levine [2] writes: "In almost half of the cases a slight or moderately loud systolic murmur can be heard,

and very rarely an aortic diastolic murmur. This latter finding was present in only one case of this entire series, and he had aortic stenosis and insufficiency. There was not a single instance of mitral stenosis in this group. In about one-half of the cases no murmur whatever could be heard." Castex [3,4] has described in cases of cardiac infarction murmurs heard during part of systole (telesystolic in contradistinction to holosystolic, heard throughout systole). Castex claims priority in having related merosystolic souffles to infarct of the myocardium. In his first article he attempts to explain the pathogenesis of the souffle as follows: "According to these findings it is logical to admit that the merosystolic souffle originates by vibration of the blood column upon contraction of the infundibular region of the left ventricle, due to the fact that the blood column finds itself in zones of different dimensions as a result of the infarct which placed a zone of that region in such a manner as to make contractions impossible. This theory explains the merosystolic souffle in the two patients and in turn is firmly based on it." In his second communication Castex refers to the experiments of Bondi who "arrived at the conclusion that most if not all of the cardiac souffles were the result of the vortex action of the blood column." . . . "According to the conception of Bondi there exists not merely one source for the souffles but there are many locations where the souffles may be produced. They may be distributed over the greater part of the internal ventricular wall. These locations are particularly numerous in the apex region of the ventricular cone." DiCio and Battro [5] report a case of painless coronary occlusion in which the diagnosis was based chiefly on the finding of a merosystolic (meso- and telesystolic) souffle. The diagnosis was confirmed at autopsy. Hyman and Parsonnet [6] write: "About one half of the patients suffering from acute coronary thrombosis exhibit cardiac murmurs. These murmurs are usually systolic in time but occasionally a diastolic blow may be heard at the base of the heart. The mechanism responsible for the establishment of these murmurs apparently is concerned with the dilatation phenomena of the heart muscle encompassing the valvular orifices. For this reason the murmurs will vary not only in their intensities but also in their duration and time factors. Indeed, it is not uncommon to observe many alterations in these three characteristics throughout but a single day." . . . "We have not been able to draw any definite conclusions in regard to prognostic information to be derived from a close study of the murmurs developing for the first time during a coronary attack. At the same time, when such murmurs are discovered and when these show characteristic alterations at each succeeding examination, certain information may be secured in regard to the state of the heart muscle. Of all the various phenomena developed by the coronary thrombosis syndrome, murmurs are unquestionably of the least importance." It will be noted that after the murmur in my case changed from a soft blowing character to one with the "zwing" of the jew's-harp there was no further change.

Dr. Fred Smith [7] says: "The damage to the papillary muscles and the mitral valve structures is an important feature in the sclerosis of the coronary arteries. The papillary muscles are likely to be involved by the occlusion of either of the main branches of the left coronary artery. The changes in these structures contribute to the alteration in the first heart sound at the apex and to the production of the systolic murmur frequently heard in this location." It occurred to

me, in considering the sequence of events in my case, that a reasonable explanation would be the location of an infarction at that point in the ventricular wall which would involve the papillary muscle, and I pictured to myself that an infarction at this point with resultant necrosis and connective tissue replacement must necessarily result in shortening of the chordae tendinae and limiting the closure of the mitral valve. We would thus have a mitral regurgitation due to organic disease though not of the mitral valve itself. This mental picture and *intra vitam* diagnosis of infarction involving the papillary muscles of the mitral valve was proved at autopsy to be correct.

Subacute Bacterial Endocarditis Complicating Coronary Infarction

White [1] lists subacute bacterial endocarditis among the complications of coronary disease. "In addition to such complications as coronary thrombosis, cardiac aneurysm, cardiac rupture, congestive failure, heart-block, and other arrhythmias, and embolism from intracardiac thrombosis, coronary disease is frequently accompanied by hyperpiesia and general arteriosclerosis, sometimes by chronic rheumatic valvular disease, diabetes, nephritis, and cerebral hemorrhage or thrombosis, and less often by luetic aortitis, thyroid disease (either thyrotoxicosis or hyperthyroidism), bacterial endocarditis, and congenital defects." The sequence in which the relationship of the two conditions is usually thought of is embolism of the coronary artery due to subacute bacterial endocarditis. It is believed that the present report is the first of an implantation of subacute bacterial endocarditis upon a heart previously damaged by infarction. It is chiefly held that subacute bacterial endocarditis occurs only in hearts in which the valves are already abnormal by reason either of a congenital anomaly or of previous inflammatory disease. In the present case the mitral valve attacked by subacute bacterial endocarditis was neither anomalous, nor had it been the site of a previous inflammatory process. Apparently, therefore, a perfectly smooth and normal valve, when handicapped by congenital anomaly or by abnormal attachment (as for example shortening of the chordae tendinae due to infarction), falls easy victim to subacute bacterial endocarditis.

I wish to point out, too, the difference between my case and those reported by C. Magarinos Torres [8] who divides his cases of parietal endocarditis into two large groups. In one of these groups parietal endocarditis is associated with valvular disease. This is what he calls valvulo-parietal endocarditis. In the other group the parietal endocarditis occurs with intact valves. This he terms genuine parietal endocarditis. In the case reported here subacute bacterial endocarditis attacked the smooth but handicapped mitral valve.

Summary

1. A case of coronary thrombosis is reported in which on the basis of a systolic murmur a diagnosis of infarction involving the papillary muscle was made. This diagnosis was substantiated at autopsy.

2. It is suggested that the occurrence of murmurs may be used as an additional means of locating the exact point of infarction on the ventricular wall.

3. The handicapped mitral valve, though free of any previous inflammatory disease and of congenital anomaly, later became the site of subacute bacterial endocarditis.

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DIABETES REFRACTORY TO INSULIN, WITH REPORT OF A CASE*

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In reviewing the literature on this subject one is struck by the fact that many cases are spoken of as "insulin refractory" which might better be termed "insulin resistant," that is, cases in which an unusually large amount of insulin must be administered in order to control the glycosuria. The case which we are reporting is truly insulin refractory; no relationship is demonstrable between the amounts of insulin given and the subsequent glycosuria.

In most instances the physiological responses to insulin are predictable, but the mechanism of its action is still problematical. The proper understanding of this mechanism is reserved for some time in the future when the etiology of diabetes mellitus shall be clear.

The theory that diabetes is the result of a functional disorder of the pancreas is based on the work of two groups. In 1889 Von Mering and Minkowski [1] showed that extirpation of the pancreas produces diabetes. In 1922 Banting and Best [2] in McLeod's laboratory demonstrated that diabetes may be controlled by the injection of insulin which is derived from the extracts of pancreatic islands.

Pathologically, typical and constant lesions characteristic of diabetes have never been found. The changes noticeable in the diabetic pancreas may also be present in the non-diabetic pancreas. Even in fatal cases of diabetes, where no pancreatic lesions are found, extraction of the gland shows the presence of insulin sufficient to continue life for several weeks. This fact and others have been advanced as evidence that one or more of the other organs in the body must have a part in the production of diabetes. The glycosuria may be due to secondary functional changes in the pancreas, or the action of the pancreas-produced insulin may be nullified by some other substance produced elsewhere in the body.

Although the hyperfunction of the thyroid has been said to impair the func-

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tional ability of the islands of Langerhans, clinically we have seen hypothyroidism co-exist with diabetes. The hypersecretion of the adrenal medulla has also been mentioned as a possible cause of diabetes, but Houssay and Lewis [3] showed that diabetes in animals follows its usual course in the absence of the adrenal medulla.

There is far more evidence to involve the pituitary than either of the mentioned organs. Colwell [4] has written a splendid review of the literature upon the relation of the hypophysis to carbohydrate metabolism, and Collip [5] more recently has pointed out the experimental, chemical, and clinical evidence for the presence of a diabetogenic factor originating in the pituitary gland. The mutually antagonistic actions of pituitary extract and insulin have been well demonstrated.

In the treatment of diabetes, when the insulin requirement exceeds the anticipated amount, we must consider the presence of a complicating condition. Pollack [6] has given a very good summary of the possibilities. Cases completely refractory to insulin, however, are not common and there are only three reported in the literature with autopsy findings. Two of these cases had pituitary tumors; the third, other diagnosable complications. Acromegaly in which there is an acidophilic adenoma of the pituitary is frequently associated with glycosuria.

Of the three cases mentioned, Mahler and Pasterny [7] report one showing inactivity of insulin in an acromegalic with glycosuria. A tumor of the hypophysis was found at autopsy.

Ulrich [8] reports a patient with a pituitary adenoma who had two attacks of pronounced glycosuria with hyperglycemia. The first period extended over a month and disappeared spontaneously. The second occurred two years later and continued until the death of the patient. Insulin had little effect on the level of the blood sugar during both of these periods.

The third case, reported by Charlton,[9] was complicated by pulmonary tuberculosis and luetic infection. The diabetes was relieved by anti-luetic treatment and the patient died of the tuberculosis.

The following case is reported because we feel that it helps to establish the relationship of the pituitary to carbohydrate metabolism.

Case Report

Mrs. M. S., colored female, aged 35, was admitted to the William J. Seymour Hospital on August 9, 1933, complaining of blindness, headaches, and "diabetes."

The patient's "diabetes" was discovered incidentally at the Henry Ford Hospital in August 1928, when she was admitted for a laceration of the dorsum of the left hand and division of the tendons of the extensor digitorum communis and extensor pollicis. The laceration was repaired, the patient was placed under a diabetic régime, and insulin was prescribed; evidently she did not follow the diabetic treatment as she did not return after the laceration was healed.

She was next seen in the Out-Patient Clinic at the Detroit Receiving Hospital on August 25, 1931 complaining of headache and blurring of vision. Examination showed a markedly decreased acuity of vision in the right eye with light perception only in the left eye. Examination of the fundi was negative. She was seen about once a month, and after one year the vision in the right eye was also reduced to light perception only.

The etiology of the amblyopia was not determined. The patient's blood Wassermann and Kahn were negative, and roentgen-rays of the skull in 1931 and again in 1932 showed no signs of an intracranial lesion. Examinations of the fundi remained

negative. She was treated with diet and insulin, but her diabetes was never controlled.

The patient said that during this time she had symptoms of polydipsia, polyuria and itching around the genitalia.

At the time of her admission to the Seymour Hospital, the patient had only light perception and was complaining of frequent distressing headaches.

In her catamenia, menses began at 13 years and were of the regular 28–4 day type. Her last menstrual period occurred two years before. Her husband and two children, 11 and 9, were all living and well.

The examination revealed a well-developed, well-nourished young colored female with constant grimacing of the face and rolling of the eyes. Both pupils were widely dilated and showed no reaction to light or accommodation; there was no evidence of cataracts. The fundus examination showed both discs to be well defined and pale although they did not appear atrophic. The arteries were small, with very little evidence of arteriosclerosis. There were no exudates or hemorrhages. The thyroid was not enlarged. The lungs were clear. The heart was normal and the blood pressure 110 mm. of mercury systolic and 70 diastolic. The abdominal examination was negative. There was no edema of the extremities. The tendon reflexes were not obtained. The neurological examination was otherwise negative.

The laboratory examinations showed: Urine, slightly cloudy and acid with a specific gravity of 1.008 to 1.025; albumin, trace; sugar, ++++; sediment (not catheterized), many white blood cells.

Blood count (August 10, 1933): hemoglobin, 12.9 grams; red blood cells, 4,500,000; white blood cells, 4,150; polynuclear neutrophiles, 37 per cent; lymphocytes, 62 per cent; monocytes, 1 per cent. Blood calcium, 9.5 mg. per cent. Blood Kahn, negative.

Spinal fluid (Dec. 20, 1933): Kahn ++++. Anti-luetic treatment in the form of iodides and bismuth was given and the spinal fluid test repeated on April 4, 1934, showing 6 cells; globulin, trace; sugar, 65 mg. per 100 c.c.; colloidal gold curve 1111221000; Kahn negative.

The glucose tolerance test on January 3, 1934 showed fasting blood, 286 mg. per cent; first hour 435; second hour 370, and third hour 350 with sugar in the urine in every specimen.

Roentgen-ray of the skull on December 9, 1933 revealed: "Sella within normal limits. No evidence of erosion. No evidence of increased intracranial pressure."

The patient was placed on a diabetic diet containing carbohydrate 100 gm., protein 70 gm., fat 150 gm. An attempt was made to adjust the insulin as shown in figure 1, gradually increasing it to 85 units daily divided into four doses. This, however, did not desugarize the patient, and her blood sugar ranged between 250 mg. and 322 mg. per 100 c.c. After 13 weeks with no success whatever in controlling the diabetes, the insulin was discontinued for two weeks, during which period the urine showed a constant glycosuria and became positive for acetone and diacetic acid and the blood sugar ranged between 272 mg. and 344 mg. per 100 c.c. The total absence of insulin made no difference in the diabetic state except for the development of a ketosis.

Insulin was started again and given every four hours throughout the 24, totaling 120 units daily for one week. There was still a glycosuria and the blood sugar ranged from 192 mg. to 286 mg. per 100 c.c. Because the patient objected to such frequent insulin injections, we administered 110 units daily in four doses for six weeks. The urine showed a glycosuria and the blood sugar ranged from 235 mg. to 286 mg. per 100 c.c. The insulin was discontinued again for two weeks during which time the urine again showed positive acetone and diacetic acid with the glycosuria. The blood sugar ranged from 323 mg. to 333 mg. per 100 c.c. Insulin was resumed in three daily doses totaling 96 units. This was continued for four weeks during which time the acetone and diacetic acid disappeared and glycosuria persisted with the blood sugar ranging from 216 mg. to 392 mg. per 100 c.c.

During this entire period the patient complained of frequent severe headaches. Because of the lack of choking of the discs or evidence of increased intracranial pressure, it was deemed advisable to investigate the head somewhat further. An encephalogram was therefore done on April 21, 1934 by Dr. F. Schreiber. The roentgen-ray showed: "No evidence of disturbance of the symmetry of the air-filled ventricular system."

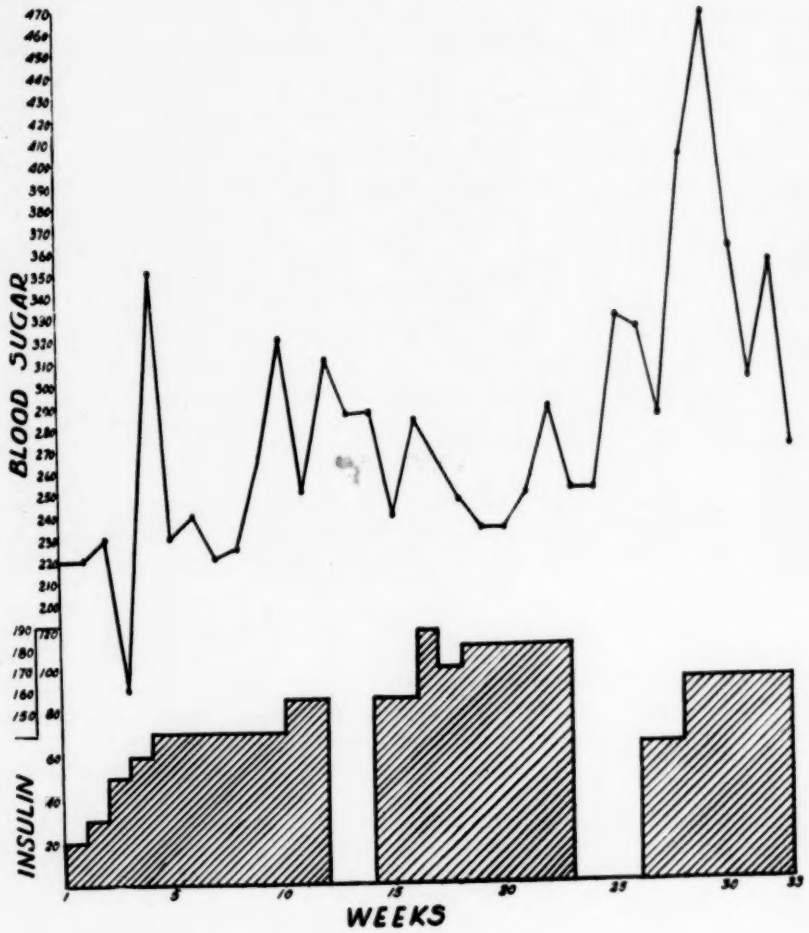

FIG. 1.

Following the performance of the encephalogram the patient vomited frequently and complained of severe headaches. Two days later she became unconscious and died on April 23, 1934. There were no clinical evidences of diabetic coma. The urine showed a one plus acetone. Blood sugar before death was 450 mg. per 100 c.c.

PATHOLOGICAL REPORT

External Appearance: The body is that of a well developed and nourished, obese, middle-aged, colored female, 165 cm. in length. The hair is black and thick. The eyes and teeth are negative. The breasts are well developed and firm. The chest is

well developed. The abdomen is moderately distended with gas. The extremities and external genitalia are negative.

Cranial Cavity: The meningeal vessels are congested. On lifting up the frontal lobes of the brain, a circumscribed oval tumor, measuring 5 cm. in length, 3 cm. in width, and 3 cm. in depth, is seen resting upon and adherent to the pituitary gland,

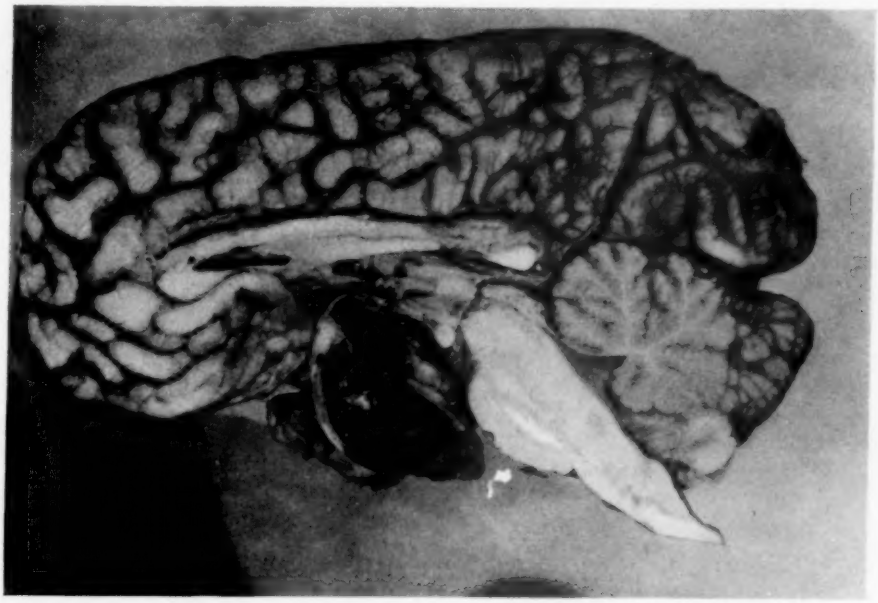

FIG. 2. Sagittal view. Note cystic structure with fibrous wall, old blood content. Hypophysis attached below.

apparently attached to the stalk and posterior lobe. The tumor lies in relation to the following structures, all of which are compressed by it: the optic chiasm superoanteriorly, the corpus callosum superiorly, and the cerebral peduncles and pons posteriorly. The arteries of the Circle of Willis are in close apposition to the tumor. Careful examination does not reveal origin of the tumor from any of the regional vessels. Upon sagittal section the tumor is seen to be free above and adherent to the pituitary below. It is cystic in nature, being distended by a dark, brownish-red, sanguineous fluid which is under moderate pressure. The walls of the cyst vary from 0.5 to 3.0 mm. in thickness, are tough and fibrous, and in some places contain bits of lime. After escape of the fluid content a soft friable, almost crumbly, dark brownish-red substance is seen. This arises from the inner lining of the cyst, over an area 1.5 cm. in diameter. The remainder of the inner lining is quite smooth, and contains a number of scattered pinpoint sized spots of a shining colorless material, which upon examination under the microscope are seen to contain cholesterin crystals. The pituitary gland is compressed and flattened. The sella turcica is definitely deepened and ballooned beyond normal limits. The brain weighs 1150 gm.

Thoracic Cavity: Both lungs are free from adhesions. The left lung weighs 400 gm. and shows a smooth pleural surface. There is superficial congestion and edema. The cut surface is deep red in color and on pressing exudes a foamy sanguineous fluid. The bronchi are injected and the pulmonary vessels congested. The right lung weighs 400 gm. and shows similar changes. The heart is soft and small, weighing 250 gm. The myocardium is congested and flabby. The left ventricle wall

measures 10 to 12 mm. in thickness, the right ventricle wall 3 to 4 mm. The valves are negative. The coronary vessels and aortic arch are negative. The trachea and larger bronchi are injected. The thoracic and abdominal portions of the aorta are negative.

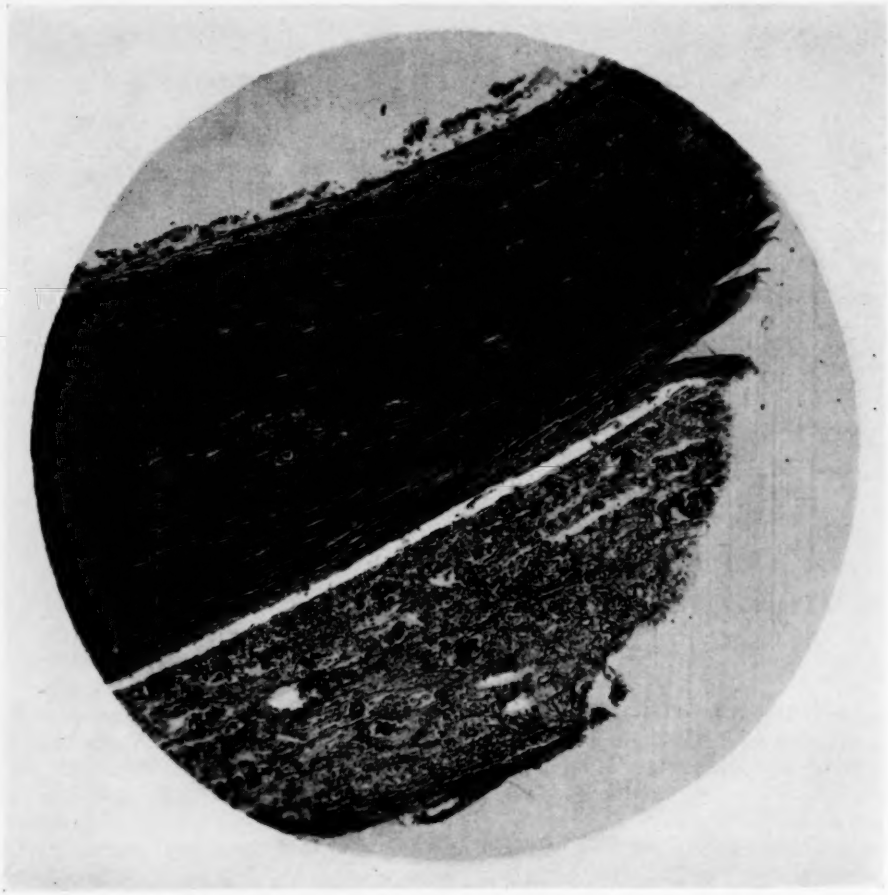

FIG. 3. Suprasellar hematoma with fibrous cyst wall compressing hypophysis.

Abdominal Cavity: The panniculus measures 5 to 6 mm. The entire bowel is distended with gas. The spleen weighs 125 grams. The capsule is grayish-blue in color and smooth. The parenchyma is soft and congested. The adrenals are of normal appearance. The kidneys each weigh 125 gm. The capsule of the left kidney strips easily exposing a smooth external surface. The cut surfaces are congested, the parenchyma very soft. The right kidney shows similar changes. The bladder, uterus, oviducts and ovaries are negative. The liver weighs 1200 gm. Externally it is smooth. The cut surface is pale brown and shows dilated central veins and irregular areas of fatty infiltration. The gall-bladder is distended with bile. The biliary tract and ampulla of Vater are negative. The esophagus, stomach, duodenum and small and large intestines are congested. The pancreas is normal in appearance.

Gross Diagnosis: Suprasellar cyst. (Craniopharyngioma?) Parenchymatous degeneration of heart, liver and kidneys. Generalized passive congestion. Moderate intestinal distention.

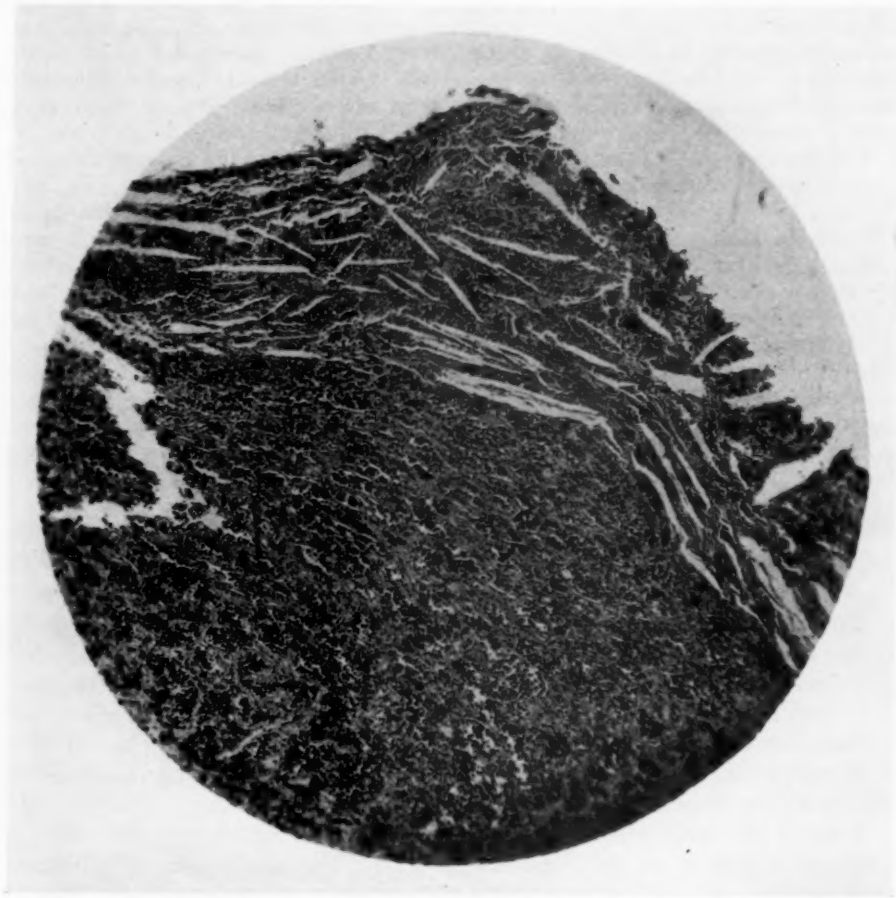

FIG. 4. Wall of hematoma showing cholesterin clefts and compressed hypophysis.

Cause of death: sudden increase of intracranial pressure resulting in compression of circulatory and respiratory centers by the tumor mass.

MICROSCOPIC EXAMINATION

The soft, friable, dark brownish-red substance within the cyst is made up of old blood and fibrin with a few scattered degenerating cells and contains a number of large cholesterin clefts. At the base of attachment to the cyst wall, this blood takes a brighter red stain. The cyst wall is made up of fibrous tissue which shows areas of fibroblastic proliferation on the inner surface, and a few areas of calcification. There are a number of regions on the inner surface showing foreign body reaction and focal accumulations of chronic inflammatory cells, consisting mainly of lymphocytes. One-fourth to one-half of the thickness of the cyst wall is made up of a

layer of epithelial cells of the anterior lobe of the hypophysis. This layer of cells lies toward the peripheral surface of the cyst wall, and consists mainly of chromophobic cells and acidophilic cells, among which the latter are prominent. Numerous chromophobic cells are seen to be undergoing degeneration, the cytoplasm having a ground glass appearance, and the nucleus being pale staining or absent. Many of the cells are disintegrating, while the outlines of others may still be recognized. In some areas groups of degenerating chromophobic cells have a foamy appearance. Due to degeneration of these cellular elements, the stroma is rendered prominent. Within the stroma, as within the fibrous tissue of the remainder of the cyst wall, there are a number of deposits of blood pigment.

The inner surface of the cyst shows no epithelial lining, and no suggestions of enamel or keratin materials.

These sections were reviewed by Dr. Carl V. Weller, Professor of Pathology, University of Michigan, whose interpretation follows: "In my opinion this is not a neoplasm. Neither is it a developmental cyst. The cystic structure here is essentially an old hematoma with a marked deposition of cholesterol and a foreign body giant-cell reaction about the cholesterol crystals. The nests of cells in the surrounding connective tissue are compressed cells from the anterior lobe and pars intermedia of the pituitary. This might well have been an aneurysm of the internal carotid artery or of the cavernous sinus or some other vascular structure; or an old hemorrhage."

Summary and Comment

This patient presents an example of diabetes entirely refractory to insulin. During the 34 weeks she was under observation the hyperglycemia and glycosuria had no relation to the amount of insulin administered. The total omission of insulin, however, resulted in a ketosis. This failure of insulin action suggests that the diabetes was not due to a dearth of insulin but that there was some factor present which had an inhibitory or antagonistic effect on both the endogenous and the exogenous insulin. At autopsy a large suprasellar cystic hematoma was found compressing the hypothalamic structure, including the anterior and posterior lobes of the hypophysis. This pathological finding points to the pituitary as the source of the antagonistic substance.

Whether this antagonistic effect is a direct one acting through the blood or on the tissue cells or on the liver is a matter for speculation and investigation. In this case no abnormal adrenal or thyroid factors were present either clinically or pathologically to suggest that the pituitary effect had come indirectly through these glands.

We are led to agree with Ulrich that the failure of insulin to produce its expected result in cases of glycosuria warrants consideration of the presence of a hypophyseal disturbance. The refractoriness to insulin may thus be considered as a diagnostic sign of the presence of a lesion in this region.

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EDITORIAL

SURGEON GENERAL CUMMING RETIRES FROM ACTIVE DUTY

THE retirement, on February 1, of Dr. Hugh S. Cumming, the fifth Surgeon General of the U. S. Public Health Service, marks the active conclusion of the distinguished career of an eminent sanitarian and public health leader. Following his graduation from the University of Virginia in 1893, Dr. Cumming entered the career corps of the Public Health Service (then called Marine Hospital Service) in 1894.

His early work consisted of a variety of assignments, including epidemic duty during yellow fever outbreaks and outbreaks of smallpox. He served at important maritime quarantine stations during the height of several yellow fever epidemics, and later served a tour of duty in the Orient. Subsequently he was placed in charge of studies of Stream Pollution Investigations with which he was occupied for a period of several years.

When Dr. Cumming was appointed Surgeon General of the Public Health Service in 1920, he entered that important office with a background of experience that was most valuable in meeting the many perplexing problems that confronted him. During the sixteen years that he served as Surgeon General of the Public Health Service he gave to that organization, as well as to the public health profession of the United States, an able leadership.

Several important and outstanding achievements mark the four terms that Dr. Cumming served as Surgeon General. Among these may be mentioned the following:

(1) The reorganization of the hospital work and expansion of the hospital facilities of the Public Health Service to meet the emergency of temporarily caring for ex-service men and women who were beneficiaries of the Veterans Administration.

(2) The completion of the National maritime quarantine system by securing transfer to Federal control of the last State-owned quarantine stations in operation, which were located at the port of New York and at several ports in the State of Texas.

(3) The establishment of a National Leprosarium for the care of lepers in the United States.

(4) The successful control of outbreaks of bubonic plague at several ports.

(5) The development and expansion of important research in field investigative activities of the Public Health Service.

(6) The improvement and development of international relations and coöperation in public health affairs.

Dr. Cumming had the unusual distinction of serving as Surgeon General under five presidents.

The Public Health Service is one of the oldest medical establishments in the Federal Government. Its origin dates from an Act of Congress approved by President John Adams on July 16, 1798. Until 1870 the principal functions of the Service were hospital care for American merchant seamen, and this work was conducted by the Treasury Department through local physicians. The first Surgeon General, Dr. John M. Woodworth, took office in 1871, and served for a period of eight years. He was succeeded by Dr. John B. Hamilton, who served for a period of twelve years. The third Surgeon General was Dr. Walter Wyman, who administered the work of the Service for a period of twenty years. Dr. Rupert Blue next served as Surgeon General for a period of eight years. Dr. Cumming, the fifth Surgeon General of the Public Health Service, served for sixteen years as administrative head of his organization.

Dr. Cumming became a Fellow of the American College of Physicians in 1923. His official duties interfered with his active participation in the annual meetings but he showed at all times a deep interest in the College. On the occasion of the Clinical Sessions in Baltimore he was instrumental in arranging as a special feature a day in Washington which included a most interesting program by members of the United States Public Health Service. Dr. Cumming was a member of the Board of Governors of the College for many years and was responsible for the proposal of a number of the officers of the Public Health Service for membership.

The medical profession and all persons interested in public health work view with extreme satisfaction the work accomplished by Dr. Cumming while serving as the head of the Public Health Service and the leader of the public health profession in this country. His ability and achievements were recognized not only throughout the United States but abroad, as he served as a member of the Health Section of the League of Nations, a member of the Permanent Committee of the International Office of Public Health, Paris, and as Director of the Pan American Sanitary Bureau. In his retirement from active service, the congratulations and best wishes of the medical profession attend him.

REVIEWS

Clinical Laboratory Methods. By PAULINE S. DIMMITT, Ph.G. 156 pages; 15 × 22 cm. F. A. Davis Company, Philadelphia. 1934. Price, $2.00.

This small book presents very concisely the most used methods of clinical pathology, bacteriology, and blood chemistry. It is composed of 148 pages, and the author has divided it into 18 chapters. The methods described are those in common use, most of them having been subjected to long and critical tests. The tests are described in simplified terms, and it has the added advantages of illustrations. The book should be of the greatest value to those who wish to perform some of the most frequently used laboratory methods which are described by the author.

J. H.

Gynecology. By BROOKE M. ANSPACH, M.D. Fifth Edition. 832 pages; 19 × 26.5 cm. J. B. Lippincott Company, Philadelphia. 1934. Price, $9.00.

The fifth edition of Anspach's textbook of Gynecology is an excellent single volume work, meeting the needs of the teacher, student and practitioner. This edition is radically changed, for in order to include many of the newer ideas in regard to endometriosis, uterine bleeding, endocrine disturbances, etc., the text had to be altered and many sections re-written.

The plan of presentation follows, in a general way, that laid down in the earlier editions. The opening chapters deal with embryology, anatomy and physiology of the generative organs, and are followed by a section devoted to examinations of the genito-urinary organs and the lower intestinal tract. The following twelve chapters are devoted to a discussion of the injuries of the pelvic floor, mal-positions of the uterus and the diseases of the external and internal generative organs, all being presented in a thorough and comprehensive manner. The chapters on ectopic pregnancy and ovarian tumor are of special interest. In addition to the affections of the generative organs, disorders of the urinary and intestinal tract are next taken up, their presentation being brief but adequate. The remaining sections are devoted to a discussion of various subjects, including backache, sterility, endocrine and menstrual disorders, irradiation therapy, pre- and post-operative preparation of the patient.

This treatise on gynecology is a practical work, clearly and concisely presented, based on the mature personal experiences of the author and on the knowledge obtained from the outstanding literary contributions of the world. The numerous illustrations, some being in color, are well selected and executed, adding greatly to the elucidation of the text. A sufficiently complete bibliography is found at the end of each chapter, which will be of aid to those desirous of more detailed information on the subject.

This work should prove of marked value to the student and practitioner, and is highly recommended.

J. M. H., JR.

Benjamin Rush, Physician and Citizen. By NATHAN G. GOODMAN. 421 pages; 16 × 23.5 cm. University of Pennsylvania Press, Philadelphia. 1934. Price, $4.00.

A solid, well documented account of the life and times of the first great physician of this country. The author deserves the gratitude of all who have been interested in the many-sided life of this medical man who was not only a medical educator, a professor of chemistry, a founder of temperance and antislavery societies, the first American psychiatrist, but also a great patriot and a courageous moulder of public

opinion in the Revolutionary period. A man of strong opinions, not unmixed with obstinacy, he made many enemies and had a historic falling out with Washington himself.

The author devotes separate chapters to various aspects of Rush's career. The account of the yellow fever epidemics is of particular interest. As a biographer the author does not yield to the modern temptation to dramatize the subject and the scene. But, if at times his narrative seems a little plodding, it is never dull and the reader feels that he is reading history and not journalism.

M. C. P.

Diseases of the Heart. By JOHN COWAN, B.A., M.D., D.Sc., F.R.F.P.S., and W. T. RITCHIE, O.B.E., M.D., F.R.C.P.E., F.R.S.E.; with a chapter on The Ocular Manifestations of Arterial Disease by ARTHUR J. BALLANTYNE, M.D., F.R.F.P.S. Third edition. xvi + 631 pages, 15 × 23 cm.; 335 illustrations. William Wood and Co., Baltimore. 1935. Price, $9.00.

This volume is not written in a particularly clear or concise fashion, and at times it seems rather disconnected. Too many briefly reported clinical cases are used to illustrate the text; often they do not particularly illuminate the point in question, and occasionally, in the reviewer's opinion, unwarranted deductions are made from such cases. There are many references to the extensive literature concerning the heart, and controversial matters are introduced without discussion adequate for a textbook. On the other hand some important viewpoints are not represented at all. High blood pressure and arteriosclerosis are not clearly separated, and there is no chapter on the former condition. In the therapeutic procedures considered will be found some which in this country are largely only of historic interest.

W. S. L., JR.

What You Should Know about Heart Disease. By HAROLD E. B. PARDEE, M.D. Second edition. 127 pages; 13.5 × 19.5 cm. Lea and Febiger, Philadelphia. 1935. Price, $1.50.

This small volume is intended to help a heart patient understand his disease. It includes an explanation of the physiology and anatomy of the heart, discussions of various types of heart disease, including the arrhythmias. Symptoms are explained and there is discussion of the outlook for a patient with heart disease. Treatment is described, including drugs. The book is recommended to the attention of physicians who feel it desirable for certain heart cases to be more fully informed concerning heart disease.

W. S. L., JR.

Krebs—im Lichte biologischer und vergleichend anatomischer Forschung. I. Band. By JOSEPH LARTSCHNEIDER, M.D. Franz Deuticke, Leipsig and Wien. 1934.

This little volume of 192 pages and 48 illustrations is the first of a series of small books on cancer, written by Dr. J. Lartschneider, giving his experiences and studies over a period of forty years. The approach, as the title indicates, is from biological and comparative anatomical research.

The author gives an historical review of cellular pathology and compares it with the older theory of humoral pathology. He emphasizes that the cancer problem is still unsolved by cellular pathology and compares the attempt to explain cancer by this means to an architect who attempts to build a building with laborers only and without material. Humoral pathology which dominated the medical world for so many centuries, he likens unto an architect who attempts to build a building with material only

and without labor. It is fortunate that humoral pathology came in contact with cellular pathology and thus collapsed. He warns, however, that cellular pathology dominates scientific medicine to the exclusion of other influences.

With these thoughts in mind, the author discusses in the first volume various aspects of the problem of epidermal cancers (Ectodermkrebs). There are 13 chapters in all, the first being on the natural history of animal skin, giving also detailed consideration of human skin. The other chapters deal with such subjects as Strict Limitation of the Concepts of Epithelium, Waldeyer's Theory of Cancer, Physiological Epithelial Fusion and Physiological Bone Fusion, Rickets, Tooth Enamel and the Work Mode of Enamel Cells during Attacks of Rickets.

All of these subjects are presented in an interesting and new light, but the work is somewhat difficult to read on account of its intense detail. It is, no doubt, a definite contribution to the cancer problem.

A second volume in two sections has been received which will be given notice in a subsequent review.

G. E. W.

COLLEGE NEWS NOTES

New Life Members

Dr. Herman O. Mosenthal (Fellow), New York City, and Dr. Carl H. Gellenthien (Fellow), Valmora, N. M., have recently become Life Members of the American College of Physicians.

Gifts to the College Library

Dr. J. C. Geiger (Fellow), Director of Public Health of the City and County of San Francisco—a copy of the manual entitled "Handbook of Accepted Remedies, Symptoms and Treatment of Poisoning; Diagnostic Procedures, and Miscellaneous Information." This manual was prepared by Dr. Geiger to serve as a guide in his department as well as for the use of the general profession.

Acknowledgment is also made of the following gifts:

Dr. Linn J. Boyd (Fellow), New York, N. Y.—a translation of Prof. August Bier's "Contributions to the Physiology and Pathology of Circulation."

Dr. Joseph Hajek (Fellow), New York, N. Y.—two reprints.

Dr. Carl R. Howson (Fellow), Los Angeles, Calif.—one reprint.

Dr. Frederick R. Taylor (Fellow), High Point, N. C.—one reprint.

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—one reprint.

State Meeting of Baltimore Members

Under the Governorship of Dr. Henry M. Thomas, Jr., Maryland members of the American College of Physicians conducted a state meeting at Baltimore on April 8, 1936. The program opened with a reception in the Board Room of the University Hospital, followed by a group of clinics in the Gordon Wilson Hall of the University Hospital and a dinner at the Hamilton Street Club. The clinical program consisted of the following papers:

"Pneumothorax Treatment of Pneumonia," Dr. Harry M. Stein; "A Case of Hair Dye Poisoning," Dr. Raymond Peters; "Conditions Simulating Coronary Thrombosis in the Electrocardiographic Findings," Dr. William S. Love, Jr.; "Hypertension Associated with Renal Tumor," Dr. J. Edmund Bradley; and "Multiple Apical Cavitations," Dr. M. C. Pincoffs.

At the dinner informal talks were given by Dr. Sydney R. Miller, past President of the College, by Dr. M. C. Pincoffs, Editor of the Annals of Internal Medicine, and by four or five other Fellows of the College. The meeting was voted a great success and plans are being made to hold the next meeting in October 1936, at the Maryland State Tuberculosis Sanatorium at the invitation of Dr. Victor Cullen (Fellow).

Under the Presidency of Dr. Chesley Bush (Fellow), Livermore, and the Chairmanship of Dr. Harold G. Trimble (Fellow), Oakland, the California Tuberculosis Association held its annual meeting in Sacramento April 2 to 4, inclusive. Dr. J. A. Myers (Fellow), associate professor of preventive medicine in the Medical and Graduate Schools of the University of Minnesota, presented a paper entitled "The Contributions of Organization." Dr. Sidney J. Shipman (Fellow), San Francisco, delivered a paper, "Tuberculous Stenosis of the Bronchus," and Dr. Edward Hayes

(Fellow), Monrovia, delivered a paper, "Relief Problems and Tuberculosis Control from the Viewpoint of a Physician." Other members of the College who officially appeared on the program as discussants of papers included Dr. Benjamin W. Black (Fellow), Oakland, Dr. F. M. Pottenger (Fellow), Monrovia, Dr. Samuel Hurwitz (Fellow), San Francisco, Dr. Charles L. Ianne (Associate), San Jose, Dr. Mumford Smith (Fellow), Los Angeles, and Dr. W. C. Voorsanger (Fellow), San Francisco.

The Illinois Tuberculosis Association held its twenty-seventh annual meeting at Decatur, April 6 to 7. Dr. D. O. N. Lindberg (Fellow), superintendent and medical director of the Macon County Tuberculosis Sanatorium, delivered a paper on "The Rôle of the Chest Roentgenogram in Tuberculosis"; Dr. Robinson Bosworth (Fellow), superintendent and medical director of the Rockford Municipal Sanatorium, "Essential Considerations Affecting the Selection of Patients Who May Profit Most from Sanatorium Treatment, and Primary Reasons for Eliminating Certain Groups from the Sanatorium." Dr. Gerald B. Webb (Fellow), chief of medical staff, Sunnyrest Sanatorium, Colorado Springs, Colo., delivered the banquet address, "An Outline of the History of Tuberculosis." Dr. Cecil M. Jack (Fellow), chairman of the Macon County Tuberculosis Sanatorium Board, presided at a luncheon and Dr. F. M. Meixner (Fellow), President of the Peoria County Tuberculosis Association, presided at the medical session.

Dr. Austen Fox Riggs (Fellow), Stockbridge, Mass., has been appointed to the staff of the Williams College health department at Williamstown.

Dr. Sigmund S. Greenbaum (Fellow) has been advanced from associate professor to professor of dermatology and syphilology, University of Pennsylvania Graduate School of Medicine.

The following Fellows appeared on the program of general assemblies of the eighth annual spring conference of the Dallas Southern Clinical Society, March 16 to 19:

Dr. Francis G. Blake, New Haven, Conn., "Treatment of Lobar Pneumonia"; Dr. Alan G. Brown, Toronto, Ont., "Meeting the Nutritional Requirements of Infancy and Childhood"; Dr. Byrl R. Kirklin, Rochester, Minn., "Diagnosis of Early Pulmonary Tuberculosis"; and Dr. John A. Kolmer, Philadelphia, Pa., "Susceptibility, Immunity and Vaccination in Infantile Paralysis."

During February, at the regular clinical pathologic conference in the Peter Bent Brigham Hospital, Boston, Dr. Henry A. Christian (Fellow), Hersey professor of the theory and practice of physic at Harvard Medical School and physician-in-chief of the Peter Bent Brigham Hospital, was presented with a volume of medical papers dedicated to him by his former students, colleagues and house officers, as a token of affection on his sixtieth birthday. Dr. Francis G. Blake (Fellow), Sterling professor of medicine at Yale University School of Medicine, New Haven, made the presentation.

Dr. Paul P. McCain (Fellow), Sanatorium, N. C., addressed the thirty-second annual meeting of the National Tuberculosis Association at New Orleans, April 22 to 25.

Dr. Lee D. Cady (Fellow), St. Louis, is President of the St. Louis Medical Society.

Dr. Marcus W. Newcomb (Fellow), Browns Mills, N. J., is President of the Medical Society of New Jersey.

Dr. F. M. Pottenger (Fellow), Monrovia, Calif., is President of the Association for the Study of Internal Secretions.

Dr. Edward Weiss (Fellow), Philadelphia, has been advanced from clinical professor to professor of clinical medicine at Temple University School of Medicine.

Dr. Edgar Erskine Hume (Fellow), librarian of the Army Medical Library, Washington, D. C., addressed the New York Academy of Medicine on "The Medical Work of the Knights of St. John of Jerusalem." The program was arranged in cooperation with the section of historical and cultural medicine.

Dr. Joseph T. Beardwood, Jr. (Fellow), Dr. Edward S. Dillon (Fellow) and Dr. Edward L. Bortz (Fellow), all of Philadelphia, addressed the New York Diabetes Association, March 20, on the clinical aspects, complications and treatment of "Diabetic Acidosis," respectively. The program of the clinical section was presented by the Philadelphia Metabolic Association.

Dr. Leonard G. Rowntree (Fellow) delivered one of the lectures, "Organotherapy from the Internist's Viewpoint," in the thirty-sixth group of Mary Scott Newbold Lectures before the College of Physicians of Philadelphia on March 4.

Dr. John B. Youmans (Fellow), associate professor of medicine, Vanderbilt University School of Medicine, Nashville, Tenn., has been appointed director of graduate courses, having special charge of courses given for practicing physicians with the coöperation of the Commonwealth Fund.

Dr. Karl D. Figley (Fellow), Toledo, Ohio, recently addressed the Chicago Society of Allergy on "Iodized Oil in Intractable Asthma."

Dr. John J. Dumphy (Fellow), Worcester, Mass., addressed the New England Heart Association February 24 on "Coronary Symptoms in Pernicious Anemia."

Announcement has been made that Dr. Raymond B. Allen, associate dean of graduate studies, Columbia University College of Physicians and Surgeons, New York, N. Y., has been appointed dean of Wayne University College of Medicine, Detroit. He will succeed Dr. Walter H. MacCraken (Fellow), who resigned a year ago. In the meantime Dr. William J. Stapleton, Jr. (Fellow), has been acting as dean. Dr. Stapleton will become associate dean.

Dr. Charles Walter Clarke (Fellow), New York City, has under his direction a special bureau in the Health Department for the control of venereal disease, functioning in connection with a campaign by the Department for the control of these diseases. An appropriation of $100,000 has been approved by the Works Progress Administration for this project.

Dr. David Riesman (Fellow), Philadelphia, delivered a lecture, "Diagnosis and Treatment of Early Circulatory Failure," in connection with the fourth annual clinical lectures of the Mercy Hospital.

Georgetown University School of Medicine has added a course in medical social economics to its curriculum of the senior year. Among lecturers on the various phases of the subject appear the following Fellows:

Dr. Arthur C. Christie
Dr. Oscar B. Hunter
Dr. Henry C. Macatee
Dr. J. Russell Verbrycke, Jr.
Dr. Wallace M. Yater

Dr. James H. Hutton (Fellow), Chicago, addressed the Chicago Society of Industrial Medicine and Surgery recently on "Endocrinology in Industrial Medicine."

Dr. Ira A. Darling (Fellow), formerly superintendent of the Warren State Hospital, Warren, Pa., has been appointed superintendent of the Springfield State Hospital at Sykesville, Md.

Dr. W. McKim Marriott (Fellow), dean and professor of pediatrics at Washington University School of Medicine, St. Louis, recently directed a two weeks' graduate course in medicine given at Washington University the latter part of April for physicians in Calhoun, Barry, Branch, Eaton, Allegan, Hillsdale and Van Buren counties and Battle Creek, Mich., provided by the W. K. Kellogg Foundation, in connection with its community health project.

Dr. Anthony Bassler (Fellow), Dr. Max Einhorn (Fellow) and Dr. Samuel Weiss (Fellow), all of New York City, have been elected honorary members of the Belgian Gastro-Enterologic Society.

Under the sponsorship of the Woman's Auxiliary of the Philadelphia County Medical Society, its sixth annual health institute was conducted on April 14. Among the speakers were the following Fellows, all of Philadelphia:

Dr. E. J. G. Beardsley, "What Life Teaches the Doctor"
Dr. Martin E. Rehfuss, "Diet After Forty"
Dr. Joseph C. Doane, "Hearts and the Family Budget"
Dr. Louis H. Clerf, "Household Aids to Health"
Dr. George E. Pfahler, "Cancer—Increasing Hope for the Patient"
Dr. Samuel B. Scholz, Jr., "Periodic Health Examinations"

Dr. George W. Covey (Fellow), Lincoln, Nebr., was inducted as President of the Nebraska State Medical Association at its annual meeting April 7.

Dr. Herbert L. Bryans (Fellow), Pensacola, Fla., is one of a number of physicians selected to participate in the weekly radio program of lectures on medical economics, sponsored by the Florida Medical Association.

Under the Presidency of Dr. James E. Paullin (Fellow), the Medical Association of Georgia held its annual session at Savannah, April 21–24. Dr. William B. Castle (Fellow), associate professor of medicine, Harvard Medical School, Boston, delivered the Abner Wellborn Calhoun Lecture on "Fundamental Aspects of the Diagnosis and Treatment of Anemia." Among other guest speakers were Dr. James S. McLester (Fellow), Birmingham, President of the American Medical Association, "Influence of the Present Day Depression Upon the Nutritive State of the American

People" and Dr. Jonathan C. Meakins (Fellow), Montreal, former President of this College, "Management of the Chronic Heart."

Dr. Carl H. Gellenthien (Fellow), Valmora, N. M., addressed the Des Moines Academy of Medicine and the Polk County Medical Society recently on "Practical Methods of Sanatorium Treatment of Pulmonary Tuberculosis."

The second annual graduate clinical meeting of the Alumni Association of the University of Buffalo School of Medicine took place April 18, and was addressed, among others, by Dr. Walter C. Alvarez (Fellow), Rochester, Minn., "Helpful Hints in the Diagnosis of Puzzling Types of Indigestion" and Dr. Ernest E. Irons (Fellow), Chicago, "Chronic Arthritis, a General Disease Requiring Individualized Treatment." Dr. Reginald Fitz (Fellow), Boston, delivered the banquet address on "The Biography of the Famous Dr. Watson of the Sherlock Holmes Stories."

Dr. William Devitt (Fellow), director of Devitt's Camp for Tuberculosis near Allenwood, Pa., has been elected President of the Pennsylvania Tuberculosis Society.

Dr. Wallace M. Yater (Fellow), Washington, D. C., Dr. William J. Kerr (Fellow), San Francisco, Calif., and Dr. Howard B. Sprague (Fellow), Boston, Mass., were among the guest speakers on the program of the twelfth annual meeting of the American Heart Association in Kansas City, May 12.

Under the Presidency of Dr. George W. Grier (Fellow), Pittsburgh, Pa., the American Radium Society held its annual meeting in Kansas City May 11 to 12. Dr. George E. Pfahler (Fellow), Philadelphia, as a former lecturer, received the Janeway Medal.

Dr. Joseph L. Miller (Fellow), Chicago, Dr. Ralph A. Kinsella (Fellow), St. Louis, Dr. Philip S. Hench (Fellow), Rochester, Minn., and Dr. William J. Kerr (Fellow), San Francisco, were among the speakers on the educational program on the differential diagnosis of diseases of joints at the meeting of the American Association for the Study and Control of Rheumatic Diseases at Kansas City, May 11.

Dr. Charles S. Holbrook (Fellow), New Orleans, has been elected Vice President of the Southern Pediatric Association.

Under the Presidency of Dr. Morris Murray Peshkin (Fellow), New York City, the Association for the Study of Allergy held its annual meeting in Kansas City, May 11 to 12.

Dr. John G. FitzGerald (Fellow), director of Connaught Laboratories and of the School of Hygiene, University of Toronto, has been appointed a member of the Permanent Commission of Biological Standardization of the Health Organization of the League of Nations.

In recognition of his achievements in science, Dr. James B. Collip (Fellow), professor of biologic chemistry, McGill University Faculty of Medicine, was presented with a gold medal by the Royal Society of Canada at a meeting in Ottawa, during February.

Dr. Ralph Pemberton (Fellow), Philadelphia, appears on the program of the fifth International Congress on Rheumatism, to be held in Lund, Sweden, September 3 to 5, and in Stockholm, September 7 to 8.

HARLOW BROOKS, M.D.

PRESIDENT OF THE AMERICAN COLLEGE OF PHYSICIANS, 1923 TO 1925

IN MEMORIAM

DR. HARLOW BROOKS

Dr. Harlow Brooks was born at Medo, Minnesota, on March 31, 1871. He received his preliminary education in the High School of Medo, and later graduated from the University of Oregon. In 1895 he received the degree M.D. from the University of Michigan School of Medicine, and from the same School received the honorary degree of M.Sc. in 1930. He took a postgraduate course of study at the University of Freiberg, and at the Polyclinic in Munich. He was Assistant Demonstrator of Anatomy at the University of Michigan School of Medicine in 1895; Instructor of Histology and Embryology, Bellevue Hospital Medical College, 1895–1898; Research in Bacteriology, New York State Hospitals, Pathological Institute, 1897–1920; Professor of Clinical Medicine, New York University Medical College, 1922–1929. At the time of his death he was Emeritus Professor of Clinical Medicine, New York University Medical College; Visiting Physician, Bellevue Hospital; Consulting Physician, New York City, French, New York Polyclinic, Union, Fifth Avenue, Hackensack, New Jersey, Beth Israel, Greenwich, Mount Vernon, Saint John's, Southside (Bay Shore), Flushing, Jamaica and Montefiore Hospitals, Hospital for Joint Diseases and Norwegian Lutheran, Deaconess's Home and Hospital. His World War record—Major, Lieut. Colonel, and Colonel, M. C., U. S. A.; Chief of Medical Service base hospital, Camp Upton; Chief Consultant in Medicine First Army Corps, A. E. F.; Senior Consultant in Medicine, Second Army Corps, A. E. F.; awarded Distinguished Service Medal and a General Citation. He was a member of the American Legion and of the Association of Military Surgeons.

He was a member of Phi Alpha Sigma fraternity; member of the Harvey Society, Society of Experimental Biology and Medicine, Association of American Physicians, American Medical Association, American Gastroenterological Association, Medical Society of the State of New York, New York County Medical Society, and the American College of Physicians. He was elected Fellow of the American College of Physicians at its first regular meeting held in New York in December 1916. He was elected President in 1923 in which capacity he served for two years. In 1925 he was elected to the Board of Regents where he served for three years; in 1929 he was elected to the Board of Governors on which he served for two years. He also served on various committees and gave generously of his time and energies to the work of the College.

Dr. Brooks was a prolific writer and published many monographs and special articles on medical and biological subjects. He was the Editor of Lippincott's Everyday Practice Series.

He was keenly interested in animal life, exploration, mountaineering and was an honorary Fellow in the New York Zoölogical Society and a

member of the Explorer's Club, Adventurer's Club, and the Camp Fire of America.

He was one of the outstanding diagnosticians of his time and was called in consultation more frequently probably than any other doctor in the United States. He was looked upon as an authority in diseases of the circulatory system. He was often referred to as the doctor's doctor, being constantly sought by his brother practitioners in cases involving their immediate families, among whom he was known as the "Beloved Physician."

Few physicians of his time gave so generously of their services to the poor.

As a young pathologist, Dr. Brooks collaborated with Dr. William Welch at Bellevue Hospital in advanced research work that resulted in the discovery of the bacillus named after Dr. Welch which is responsible for the disease commonly called gas bacillus infection, and which, by a curious coincidence, was the cause of his death.

One of the contributing factors which enabled Dr. Brooks to maintain his enthusiasm for his profession and for life in general was his devotion to his hobbies which were varied. He was a skilled musician and a collector of outstanding works of art, as well as an anthropologist of note. His collection of Indian relics surpassed any similar private collection in the world, containing a few specimens not to be found in any other collection.

Probably his great physical stamina was due, in part at least, to his love for fishing and hunting, in each of which he was an outstanding expert. Often Dr. Brooks would remark that he gladly devoted ten months each year to the pursuit of his profession but retained two months to seek recuperation and happiness in the great open spaces.

One of the outstanding characteristics of this great physician was his genius for friendship. His friendship was a living vital force upon which rested profound gratification and innermost happiness. When Dr. Brooks bestowed his friendship it was for the duration of life. He was truly catholic in these friendships which were confined to no one profession or social stratum. Caring little for individual accomplishments, Dr. Brooks demanded honesty, frankness, and I was about to add, loyalty in his friends. However, since loyalty is the quintessence of true friendship it may be omitted.

I have somewhat stressed this phase of Dr. Brooks' character because to him it was the dominating influence of his life, and also because in these times of emotional upheaval and cross purposes the gift of true friendship is a God given talent which is all too rare.

And so from out of our midst has been taken this great physician, this talented gentleman, this indefatigable worker, this scientist of renown, this man of many enthusiasms, of loyal friendships, of kindly heart and broad sympathies—gifted in so many ways and with so many talents that the world is richer for his having lived in it. Those who had the privilege of close

association with Dr. Brooks will carry ever in their hearts the memory of his cheering and inspiring presence and the light of his Christian spirit.

WILLIAM GERRY MORGAN.

OBITUARIES

DR. CHRISTOPHER M. REYHER

Dr. Christopher M. Reyher (Fellow), of Gary, Indiana, met a tragic death in the path of a speeding train on February 12, 1936.

Dr. Reyher was born at Garrett, Ind., in 1881. He received his medical degree from Northwestern University Medical School in 1906. For many years he was engaged in general practice, but later specialized in pediatrics. He was a member of the staffs of the Mercy and Methodist Hospitals, Gary, Ind.; a member of the Lake County Medical Society, Indiana State Medical Association and the American Medical Association. He became a Fellow of the American College of Physicians in 1925. He served as Secretary and later as President of the Board of Health of Gary and during his ten years in office made many important contributions to the public welfare.

Dr. Reyher was one of the best loved and most respected members of the medical profession in Gary. His death brought forth expressions of regret and of tribute from all his colleagues as well as from a great host of patients to whom he had ministered during his twenty-six years of practice in that community.

DR. EDWARD QUINTARD

Dr. Edward Quintard (Fellow), New York, N. Y., physician and man of letters, died suddenly at the age of sixty-nine years on February 12, 1936. in Chattanooga, Tenn., where he had gone to attend a meeting of the Board of Regents of the University of the South. Dr. Quintard was a graduate of Columbia University College of Physicians and Surgeons, 1887. He was emeritus professor of medicine and consulting physician to the New York Postgraduate School and Hospital. His influence and vision helped to guide this institution in its infancy. After a broadly cultural education both here and in Europe, Dr. Quintard first became attached to the New York Postgraduate School as clinical assistant. He was rapidly promoted through the various grades and became professor of medicine in 1904. He had also served as director of the department of medicine for many years. Also, in 1904, he was elected a member of the Board of Directors and served as Vice President until his retirement in 1918. He was a member of his local and national societies and had been a Fellow of the American College of Physicians almost from its inception, dating back to 1917. He made many important contributions to medical literature.

His death brought personal sorrow to a large number in every walk of life. Always a lover of good fellowship, Dr. Quintard by his enthusiasm

and his mellow personality endeared himself to all who worked with him. In the latter years of his life, he gave great beauty to the world in his writing and painting, and was able to devote much time to literary and philosophical pursuits.

Selected, in part, from a resolution of the Board of Directors of the New York Postgraduate Hospital and furnished through the courtesy of Walter W. Palmer, M.D., F.A.C.P., Governor for eastern New York.

DR. ALBERT HARRISON BRUNDAGE

Dr. Albert H. Brundage (Fellow) of Woodhaven, Queens County, N. Y., died March 12, 1936, after many years of impaired health; aged seventy-three.

Dr. Brundage was born at Candor, Tioga County, New York, March 3, 1862. He graduated from the New York University Medical College in 1885. He held the additional degrees of A.M., Ph.G., Phar.D. and M.S. He was particularly interested in toxicology, being the author of " A Manual of Toxicology." For the last several years he had been consulting toxicologist in the Bushwick Hospital, medical inspector and lecturer in the Department of Health of the City of New York and a member of the auxiliary staffs of the Lutheran and Jamaica Hospitals. He became a Fellow of the American College of Physicians in 1929.